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REVIEW ARTICLES

Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment

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Introduction: This systematic review provides supporting evidence for the accompanying clinical practice guideline on the treatment of restless legs syndrome and periodic limb movement disorder.

Methods: The American Academy of Sleep Medicine commissioned a task force of experts in sleep medicine. A systematic review was conducted to identify studies that compared the use of pharmacological or nonpharmacological treatment to no treatment to improve patient-important outcomes. Statistical analyses were performed to determine the clinical significance of using various interventions to treat restless legs syndrome and periodic limb movement disorder in adults and children. The Grading of Recommendations Assessment, Development, and Evaluation process was used to assess the evidence for making recommendations.

Results: The literature search resulted in 3,631 studies out of which 148 studies provided data suitable for statistical analyses. The task force provided a detailed summary of the evidence along with the certainty of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations.

Keywords: restless legs syndrome, periodic limb movement disorder, Willis-Ekbom disease, sleep-related movement disorders

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INTRODUCTION

This systematic review provides supporting evidence for the accompanying clinical practice guideline[1] on the treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) in adults and children. This systematic review is an update to the previously published American Academy of Sleep Medicine (AASM) guideline on the treatment of RLS and PLMD in 2012.[2]

RLS is characterized by an uncomfortable urge to move, often associated with dysesthesias in the affected extremity, which occurs when at rest, predominantly in the evening and/or at night and is relieved temporarily with movement.[3] It often results in difficulty falling and/or staying asleep. The identification of pediatric RLS poses specific challenges as children do not always present with the typical symptoms of leg discomfort or "urge" to move the legs. Instead, they express symptoms with their own words or actions (rubbing or scratching their legs), often leading to delays in diagnosis and treatment.[4]

The aims of the present systematic review are to assess (1) the efficacy of pharmacologic and nonpharmacologic interventions for the treatment of RLS and PLMD in both adults and children as well as in special populations such as chronic kidney disease/end-stage renal disease (ESRD), (2) to evaluate the potential for adverse effects of these interventions, and (3) to identify gaps in the treatment research literature and offer recommendations for optimizing quality and uniformity of future investigations.

RLS is a disorder with both variable chronicity (from time limited to chronic) and severity (from occasional and mild to daily and severe). Roughly 2–3% of adults in the United States and Europe have clinically important symptoms occurring at least twice per week with at least moderate distress. RLS affects approximately 2% of children.[4] For these individuals, the need for chronic RLS medical therapy is common. While our understanding of the efficacy of medical treatments for RLS as well as its pathophysiology have increased substantially in the past 2–3 decades, RLS treatment is currently perhaps most challenged by a delay in the change of clinical practice as this new information has emerged. This systematic review and its accompanying clinical practice guideline[1] aim to align clinical practice and current evidence on the medical treatment of RLS and PLMD.

The development of new medications for the treatment of RLS has been slowed by our limited understanding of its pathophysiology. Despite this, several evidence-based treatments with distinct mechanisms of action exist, with demonstrated efficacy and unique side effect profiles. The alpha-2-delta ligands, gabapentin, gabapentin enacarbil, and pregabalin, have efficacy in treating RLS, putatively through a mechanism of decreased glutamate release.[5] Brain iron deficiency, specifically in the striatum, appears central in the pathogenesis of RLS, having been demonstrated in imaging and postmortem studies, potentially explaining the efficacy of iron administration.[6,7] On the other hand, excess striatal dopamine appears to be secondary to brain iron deficiency.[8,9] Despite dopamine being in excess in RLS, all dopaminergic agents are very effective, at least initially, in treating RLS symptoms. Over time, however, dopaminergic medications are commonly associated with a paradoxical worsening of RLS, a phenomenon termed augmentation.[10] This exposes a pathophysiology-treatment mismatch as the approach of using dopaminergic medications to treat RLS was popularized during a time when the prevailing thought was that RLS was caused by a reduction of dopamine.[11] Studies assessing treatment options in children are scarce, and treatment usually consists of lifestyle modifications, iron supplementation, and possibly off-label medications.

Our understanding of RLS pathophysiology has been aided by its clinical responsiveness to low-dose opioids. This clinical observation made over 30 years ago has guided research which demonstrates reductions in the endogenous opioid, β-endorphin, in postmortem brains of patients with RLS as well as in recent cerebrospinal fluid studies, perhaps validating the use of opioids to treat RLS.[12–14] Other treatment options include peroneal nerve stimulation and dipyridamole. The diverse pharmacology of agents effective in treating RLS reflects the complexity of RLS pathophysiology, which despite much work, still needs clarification. Thus, it is likely and needed that other treatments for RLS which target novel biologic pathways could emerge.

Those with RLS may have frequent periodic limb movements during sleep (PLMSs) but, by definition, cannot have PLMD; the diagnoses of RLS and PLMD are mutually exclusive. PLMD consists of PLMS with resulting sleep disruption and/or daytime dysfunction, all occurring in the absence of RLS.[15] PLMS may present differently in young children as isolated or nonperiodic limb movements but when present, PLMS in children have shown, similarly to adults, high night-to-night variability, contributing to challenges in their identification and quantification.[16]

PLMD is a diagnosis of exclusion which requires that specific other sleep disorders (narcolepsy, untreated obstructive sleep apnea, rapid eye movement sleep behavior disorder, or RLS) cannot be present, and that medical, neurological, and psychiatric disorders cannot better explain the PLMS, nocturnal sleep disruption, or daytime dysfunction. Given the necessity of this extensive clinical evaluation, which is often not performed in clinical practice or in research studies, the true prevalence of PLMD remains uncertain. Beyond this, there are few, if any, high-quality randomized clinical trials for PLMD treatment, and only a small portion of the systematic review will discuss treatment of PLMD.

This systematic review provides supporting evidence for the accompanying clinical practice guideline[1] for the treatment of RLS and PLMD in adults and children. It provides details on outcomes and adverse effects related to different treatments that the task force (TF) reviewed in order to develop the proposed guidelines, but that were not included in the guideline proper. Treatment and adverse event outcomes were considered and categorized as critical or important. All outcomes are listed below under patient, intervention, comparison, and outcomes (PICO) questions (**Table 1**). Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to determine guidelines based upon assessment of 4 components: certainty of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described in more detail below.

METHODS

Expert TF

The AASM commissioned a TF comprised of board-certified sleep medicine specialists with proficiency in the treatment of adults and children with RLS and PLMD to develop this systematic review. The TF was required to disclose all potential conflicts of interest per the AASM's conflicts of interest policy prior to being appointed to the TF, and throughout the research and writing of this paper. In accordance with the AASM's conflicts of interest policy, TF members with a level 1 conflict were not allowed to participate. TF members with a level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interests are listed in the Disclosure Statement.

PICO questions and clinical significance thresholds (CSTs)

PICO questions were developed to assess the efficacy of interventions based on a review of the existing AASM practice parameters on the treatment of RLS and PLMD, and a review of systematic reviews, meta-analyses, and guidelines published since 2012. The AASM Board of Directors approved the final list of PICO questions presented in **Table 1** before the literature searches were conducted. Through consensus, the TF then

Table 1—PICO questions.

1	**Population:** Adults with RLS
	Intervention: Pharmacological and nonpharmacological treatments
	Comparison: Placebo or no treatment
	Outcomes: Disease severity, sleep quality, QOL, sleep latency, WASO, PLM frequency, adverse effects
2	**Population:** Adults with RLS and ESRD
	Intervention: Pharmacological and nonpharmacological treatments
	Comparison: Placebo or no treatment
	Outcomes: Disease severity, sleep quality, QOL, sleep latency, WASO, PLM frequency, adverse effects
3	**Population:** Adults with PLMD
	Intervention: Pharmacological and nonpharmacological treatments
	Comparison: Placebo or no treatment
	Outcomes: Sleep quality, QOL, excessive daytime sleepiness, WASO, PLM frequency, adverse effects, work/school performance
4	**Population:** Children with RLS
	Intervention: Pharmacological and nonpharmacological treatments
	Comparison: Placebo or no treatment
	Outcomes: Disease severity, sleep quality, QOL, PLM frequency, adverse effects, work/school performance, resolution of ADHD symptoms
5	**Population:** Special populations of children with RLS
	Intervention: Pharmacological and nonpharmacological treatments
	Comparison: Placebo or no treatment
	Outcomes: Disease severity, sleep quality, QOL, fatigue, PLM frequency, adverse effects, resolution of ADHD symptoms
6	**Population:** Children with PLMD
	Intervention: Pharmacological and nonpharmacological treatments
	Comparison: Placebo or no treatment
	Outcomes: Sleep quality, QOL, excessive daytime sleepiness, PLM frequency, adverse effects, work/school performance, resolution of ADHD symptoms

ADHD = attention deficit hyperactivity disorder, ESRD = end-stage renal disease, PICO = patient, intervention, comparison, and outcomes, PLM = periodic limb movement, PLMD = periodic limb movement disorder, QOL = quality of life, RLS = restless legs syndrome, WASO = wake after sleep onset.

developed a list of patient-oriented, clinically relevant outcomes to determine the efficacy of the interventions. These outcomes were also identified through stakeholder surveys which included input from relevant professional organizations and patient advocacy groups. The TF rated the relative importance of each outcome to determine which outcomes were critical vs important for decision-making. A summary of these outcomes by PICO is presented in **Table 2**.

The TF set a CST for each outcome to determine whether the mean differences between treatment and control or before and after treatment in the outcomes assessed were clinically significant. Standardized mean differences were used when the TF concluded that the interpretation of effect sizes would be more meaningful. The CST was defined as the minimum level of improvement in the outcome of interest that would be considered clinically important to clinicians and patients. CSTs were determined based on a TF literature review of commonly used thresholds. When no clearly established threshold values could be determined, the TF used their clinical judgment and experience to establish a CST based on consensus. A summary of the CSTs for the clinical outcome measures is presented in **Table 3**.

When considering RLS severity, priority was given to the International RLS Study Group Severity scale (IRLS) scores. The IRLS scale is the most frequently used scale to assess severity of RLS and treatment effects.

Literature searches, evidence review, and data extraction

The TF performed an extensive review of the scientific literature to retrieve articles that addressed the PICO questions. Literature searches were performed by the TF to address each PICO question using the PubMed database (see **Figure 1**). The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material.

The initial literature search in PubMed was performed in October 2019. Additional searches were performed in April 2021, August 2022, and August 2023 to update the evidence during completion of the draft. These searches identified a total of 3,728 articles. Lastly, the TF reviewed previously published guidelines, systematic reviews, and meta-analyses to spot check for references that may have been missed during the prior searches. The TF identified 26 additional articles that were screened for inclusion/exclusion in the guideline.

The TF set inclusion and exclusion criteria, which are presented in the supplemental material. All studies were reviewed based on inclusion/exclusion criteria by 2 TF members.

Table 2—Outcomes by PICO question.

Outcomes	PICO Question					
	1	2	3	4	5	6
Excessive sleepiness			√*			√
Disease severity	√*	√*		√*	√	
Quality of life	√*	√*	√*	√*	√*	√*
Sleep quality	√*	√*	√*	√*	√*	√*
Sleep latency	√	√				
WASO	√	√	√			
Fatigue					√	
Work/school performance			√*	√		√*
Resolution of ADHD symptoms				√	√	√
PLM frequency	√	√	√	√	√	√
Adverse effects	√*	√*	√*	√*	√*	√*

*Outcomes considered critical for decision-making. ADHD = attention deficit hyperactivity disorder, PICO = patient, intervention, comparison, and outcomes, PLM = periodic limb movement, WASO = wake after sleep onset.

Any discrepancies between the reviewers were discussed and resolved by the 2 reviewers or a third TF member. A total of 125 studies were determined to be suitable for meta-analysis and/or grading.

Statistical methods, meta-analysis, and interpretation of clinical significance

Meta-analysis was performed on outcomes of interest, when possible, for each PICO question (see **Table 1**). Comparisons of interventions to controls and/or assessment of efficacy before and after treatment of RLS or PLMD were performed. The analyses were performed using Review Manager 5.3 software by pooling data across studies for each outcome measure. Posttreatment data from each arm were used for meta-analysis of randomized controlled trials (RCTs) when change values were not reported and baseline values between the 2 study groups were statistically similar. Pre- and posttreatment data were used for meta-analyses of observational studies. The pooled results for each continuous outcome measure were usually expressed as the mean difference between the intervention and control for RCTs or pretreatment vs posttreatment for observational studies; however, for some outcomes where individual component scales were pooled, a standardized mean difference or effect size was determined. The pooled results for dichotomous outcome measures were expressed as the risk ratio or risk difference between the intervention and comparator or pre- vs posttreatment. The relative risk data were converted to an absolute risk estimate expressed as the number of events/1,000 patients treated. All analyses were performed using a random effects model with results displayed as a forest plot. Interpretation of clinical significance for the outcomes of interest was conducted by comparing the mean difference in effect size, or the risk difference for dichotomous outcomes, of each treatment approach to the CST (see **Table 3**).

GRADE assessment for developing recommendations

The assessment of evidence quality was performed according to the GRADE process.[17,18] The TF assessed the following 4 components to determine the direction and strength of a recommendation: certainty of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below.

1. Certainty of evidence: Based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (95% confidence interval [CI] crosses the CST and/or sample size < 100 participants), inconsistency ($I^2 \geq 50\%$), indirectness (study population vs target patient population), and risk of publication bias, the TF determined their overall confidence that the estimated effect found in the body of evidence was representative of the true treatment effect that typical patients with RLS or PLMD would see. The quality of the evidence was based on outcomes that the TF deemed critical for decision making; important outcomes are not considered when determining the overall certainty of evidence.
2. Benefits vs harms: Based on the meta-analysis of adverse effects reported within the accepted literature and on the clinical expertise of the TF, the TF determined whether the beneficial outcomes of using each intervention outweighed any harms.
3. Patient values and preferences: Based on the clinical expertise of the TF members and any data published on the topic relevant to patient preferences, the TF determined whether patient values and preferences would be generally consistent across most patients, and whether patients would use the intervention based on the relative harms and benefits identified.
4. Resource use: Based on the clinical expertise of the TF members, the TF determined whether the accessibility

Table 3—Summary of clinical significance thresholds for outcome measures.

Outcome Measure	Clinical Significance Threshold*†
Excessive sleepiness	—
ESS	−2 points[19,20]
QOL	—
RLS-QOL (Abetz)	+5 points
RLS-QOL (Kohnen)	−2.5 points
RLS-QLI	+5 points[21]
Sleep quality	—
PSQI	−3 points[22]
MOS	SMD = 0.2
Disease severity	—
IRLS‡	−3 points
RLS-6	SMD = 0.2
CGI-I	15% responders
CGI-S	0.5 points
PGI-I	15% responders
JHRLSS	+1 point
ASRS	−3 points
Sleep latency (PSG)	−10 minutes
WASO (PSG)	−10 minutes
Fatigue	—
FSS	−0.25 points
SF-36 vitality	+5 points
PLM frequency	—
PLMI	—
School/work performance	—
WPAI	—
GPA	−1 point
Attendance	−30%
Adverse effects	—
Adverse events leading to study withdrawal	50/1,000 patients
Specific adverse events	50/1,000 patients
Resolution of ADHD symptoms	—

*References used to inform TF consensus. †The clinical significance thresholds are for comparison of pre- versus posttreatment effects as well as between intervention and control. ‡TF gave higher value to the IRLS scale for disease severity. ADHD = attention deficit hyperactivity disorder, ASRS = adult attention deficit hyperactivity disorder self-report scale, CGI-I = clinical global impressions-improvement scale, CGI-S = clinical global impressions-severity scale, ESS = Epworth Sleepiness Scale, FSS = fatigue severity scale, GPA = grade point average, IRLS = International Restless Legs Syndrome Study Group Rating Scale, JHRLSS = Johns Hopkins Restless Legs Severity Scale, MOS = medical outcomes sleep scale, PGI-I = patient global impression of improvement scale, PLM = periodic limb movement, PLMI = periodic limb movement index, PSG = polysomnography, PSQI = Pittsburgh Sleep Quality Index, QOL = quality of life, RLS = restless legs syndrome, RLS-6 = restless legs syndrome-6 scale, RLS-QLI = restless legs syndrome quality of life instrument, RLS-QOL = restless legs syndrome quality of life, SF-36 = 36-item short form health survey questionnaire, SMD = standardized mean difference, TF = task force, WASO = wake after sleep onset, WPAI = work productivity and activity impairment questionnaire.

and costs associated with each treatment approach compared favorably to those associated with alternative treatments. Information on costs to both patients and the health care system, impact on health equity, acceptability and feasibility to implement the treatments were considered.

A summary of each GRADE domain is provided after the detailed evidence review.

Public comment and final approval

A draft of the guideline and systematic review was made available for public comment for a 4-week period on the AASM website. The TF took into consideration all the comments received and made decisions about whether to revise the draft based on the comments. The revised guideline and systematic review were submitted to the AASM Board of Directors for subsequent approval.

The AASM expects this systematic review to have an impact on professional behavior, patient outcomes, and possibly health care costs. This review reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

RESULTS

The aims of the current literature reviews and data analyses were focused on addressing 6 questions to assess the efficacy of various interventions to treat RLS and PLMD. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. All figures and a summary of the study characteristics can be found in the supplemental materials. All values of the critical outcomes results are reported in the following text. For important outcomes results, values are only reported if the results met the CST. Each evidence summary is accompanied by a discussion of the certainty of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the recommendations provided in the accompanying clinical practice guideline.[1] The interventions below are listed in alphabetical order.

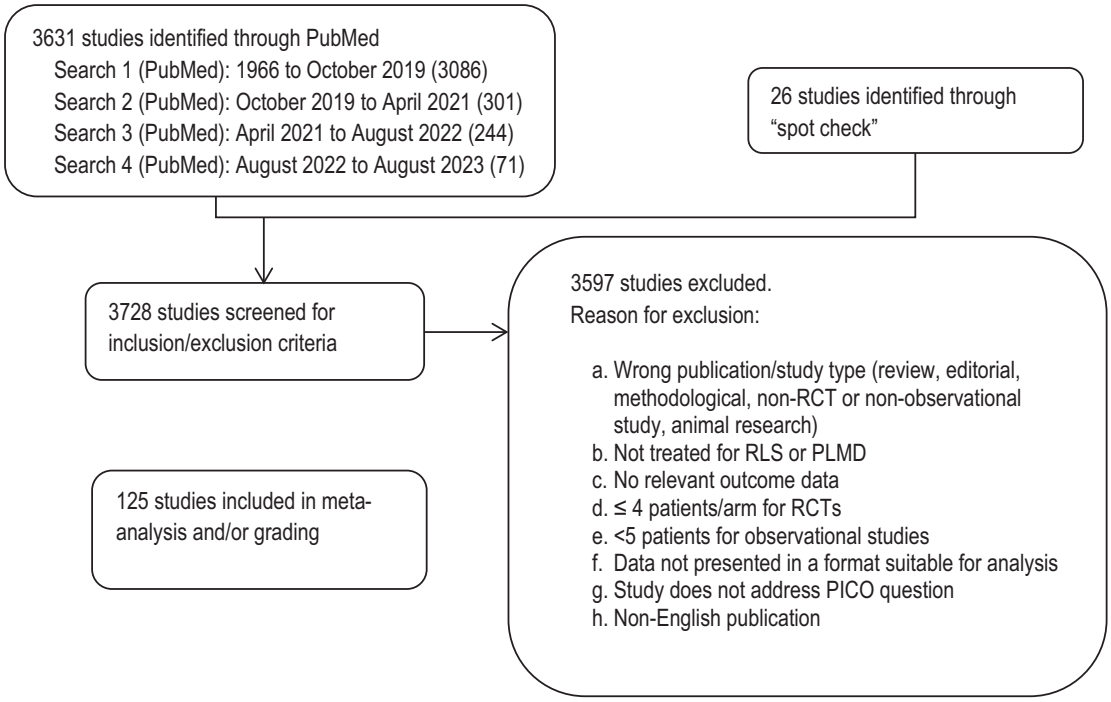
The following interventions are those for which recommendations were made in the accompanying clinical practice guideline.[1]

PICO 1: ADULTS WITH RLS

Gabapentin enacarbil

A total of 8 RCTs[23–30] and 2 observational studies[31,32] investigated the use of gabapentin enacarbil in adults with RLS to improve 1 or more of the following outcomes: disease severity, quality of life (QOL), sleep quality, sleep latency, wake after sleep onset (WASO), periodic limb movement (PLM) frequency, and unwanted side effects. Participants in the RCTs had a mean age of 50 years (56% female) and were diagnosed with moderate to severe RLS. Participants received dosages of

Figure 1—Evidence base flow diagram.



PICO = patient, intervention, comparison, and outcomes, PLMD = periodic limb movement disorder, RCT = randomized controlled trial, RLS = restless legs syndrome.

gabapentin enacarbil from 600–2,400 mg. Three of the trials used a crossover design, with patients serving as their own controls, and the remaining 5 trials had separate placebo control groups. The observational studies were before-and-after treatment design investigating participants with moderate-to-severe RLS, receiving dosages of 300–1,500 mg. Meta-analyses were performed to assess the efficacy of gabapentin enacarbil as a treatment for adults with RLS. The meta-analyses are provided **Figure S1** through **Figure S19** in the supplemental material. A summary of findings table is provided in **Table S1**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of gabapentin enacarbil to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

Disease severity: The efficacy of gabapentin enacarbil to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 7 RCTs[23,25,26,28–30,33] including a total of 1,511 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −4.93 points (95% CI: −6.85 to −3.02 points) as measured by the IRLS (see **Figure S1**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the IRLS was also evaluated using a meta-analysis of 2 observational studies[31,32] of 148 participants. The duration of patient follow-up after treatment ranged from 8–52 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −12.64 points (95% CI: −24.53 to −0.76 points) as measured by the IRLS (see **Figure S2**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the clinical global impressions-improvement scale (CGI-I) was evaluated using a meta-analysis of 7 RCTs[24–30] in 1,632 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 34% (95% CI: 24–45%) as measured by the CGI-I (see **Figure S3**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the CGI-I was also evaluated using a meta-analysis of 2 observational studies[31,32] in 443 participants. The duration of patient follow-up after treatment ranged from 12–52 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 83% (95% CI: 76–90%) as measured by the CGI-I (see **Figure S4**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the patient global impression (PGI) was evaluated using a meta-analysis of 5 RCTs[14,25–27,33] in 1,061 participants. The duration of patient follow-up after treatment ranged from 3–12 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants

whose symptoms responded to treatment of 34% (95% CI: 16–53%) as measured by the PGI (see **Figure S5**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the PGI was also evaluated using a meta-analysis of 2 observational studies[31,32] in 440 participants. The duration of patient follow-up after treatment ranged from 12–52 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 83% (95% CI: 76–91%) as measured by the PGI (see **Figure S6**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the clinical global impressions-severity scale (CGI-S) was evaluated using an analysis of 1 RCT[17] in 78 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant decrease in disease severity of −1.20 points (95% CI: −1.67 to −0.73 points) as measured by the CGI-S (see **Figure S7**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the RLS-6 was evaluated using an analysis of 1 RCT[17] in 78 participants. The duration of patient follow-up after was 2 weeks. The analysis demonstrated a clinically significant decrease in disease severity reporting a standardized mean difference of −0.45 (95% CI: −0.90 to −0.0) as measured by the RLS-6 (see **Figure S8**).

The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

QOL: The efficacy of gabapentin enacarbil to improve QOL was evaluated from an analysis of 1 RCT[19] that reported on the RLS-QOL Abetz scale in 221 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a clinically significant improvement in QOL of 7.30 points (95% CI: 2.78–11.82) as measured by the RLS-QOL Abetz scale (see **Figure S9**). The certainty of evidence was moderate due to imprecision.

Sleep quality: The efficacy of gabapentin enacarbil to improve sleep quality was evaluated based on an analysis of 1 RCT[17] that reported on the Medical Outcomes Study Sleep (MOSS) scale in 78 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant improvement reporting a standardized mean difference of 0.59 (95% CI: 0.14–1.04) as measured by the MOSS scale (see **Figure S10**). The certainty of evidence was moderate due to imprecision.

Adverse effects: A meta-analysis of 8 RCTs[23,25–30,33] reported on the total adverse events that led to study withdrawal in a total of 1,729 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of adverse events leading to study withdrawal of 2.2 (95% CI: 1.21–3.98) with an absolute risk of 48 events/1,000 patients (95% CI: 26–87 events/1,000 patients) with use of gabapentin enacarbil (see **Figure S11**).

A meta-analysis of 2 observational studies[31,32] reported the risk of unwanted side effects and total adverse events that led to study withdrawal in 508 participants. The duration of patient follow-up after treatment ranged from 12–52 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.13 (95% CI: 0.10–0.16) with an absolute risk of 130 events/1,000 patients (95% CI: 10–16 events/1,000) with use of gabapentin enacarbil (see **Figure S12**).

A meta-analysis of 8 RCTs[23,25–30,33] reported on the incidence of somnolence in a total of 1,733 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of somnolence of 3.41 (95% CI: 1.92–6.05) with an absolute risk of 176 events/1,000 patients (95% CI: 66–366 events/1,000 patients) with use of gabapentin enacarbil (see **Figure S13**).

An analysis of 1 observational study[32] reported on the incidence of somnolence in 182 participants. The duration of patient follow-up after treatment was 52 weeks. The analysis demonstrated a clinically significant risk difference of 0.41 (95% CI: 0.34–0.48) with an absolute risk of 410 events/1,000 patients (95% CI: 340–480 events/1,000) with use of gabapentin enacarbil (see **Figure S14**).

A meta-analysis of 8 RCTs[23,25–30,33] reported on the incidence of dizziness in a total of 1,733 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of dizziness of 4.57 (95% CI: 3.07–6.80) with an absolute risk of 150 events/1,000 patients (95% CI: 87–241 events/1,000 patients) with use of gabapentin enacarbil (see **Figure S15**).

An analysis of 1 observational study[32] reported on the incidence of dizziness in 182 participants. The duration of patient follow-up after treatment was 52 weeks. The analysis demonstrated a clinically significant risk difference of 0.46 (95% CI: 0.39–0.53) with an absolute risk of 460 events/1,000 patients (95% CI: 390–530 events/1,000) with use of gabapentin enacarbil (see **Figure S16**).

The certainty of evidence for unwanted side effects ranged from high to low due to risk of bias associated with observational studies and imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of gabapentin enacarbil: PLM frequency, sleep latency, and WASO.

PLM frequency: The efficacy of gabapentin enacarbil to decrease PLM frequency was evaluated using a meta-analysis of 2 RCTs[26,30] in 330 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. The meta-analysis demonstrated a decrease of −8.38 PLMs/h (95% CI: −14.03 to −2.72 PLMs/h) as measured by the periodic limb movement index (PLMI) (see **Figure S17**). The CST for this outcome was not determined as the TF could not reasonably estimate a threshold for this measure.

Sleep latency: The efficacy of gabapentin enacarbil to decrease sleep latency was evaluated using a meta-analysis of 2 RCTs[26,30] in 330 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. Meta-analysis demonstrated a nonclinically significant decrease of −2.44 minutes

(95% CI: −8.16 to 3.28 minutes) (see **Figure S18**). The certainty of evidence was moderate due to imprecision.

WASO: The efficacy of gabapentin enacarbil to decrease WASO was evaluated using a meta-analysis of 2 RCTs[26,30] in 330 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of −28.34 minutes (95% CI: −39.91 to −16.77 minutes) with gabapentin enacarbil (see **Figure S19**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of gabapentin enacarbil in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S1**).

Benefits vs harms

The potential benefits of gabapentin enacarbil in adults with RLS include a clinically significant improvement in disease severity, QOL, sleep quality, and WASO. The potential harms include a clinically significant risk of somnolence and dizziness that may or may not resolve over time. Other side effects including headache, nasopharyngitis, nausea, fatigue, diarrhea, and vertigo have been reported. The TF judged that the potential benefits of gabapentin enacarbil in adults with RLS outweigh the potential harms.

Resource use

The current unit costs for gabapentin enacarbil is $14.45 for a 300 mg tablet and $14.41 for a 600 mg tablet.[34] The TF judged these costs are large.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally be accepting of treatment with gabapentin enacarbil.

Gabapentin

A total of 2 RCTs[34–36] and 4 observational studies[37–40] investigated the use of gabapentin in adults with RLS to improve 1 or more of the following outcomes: disease severity, QOL, sleep quality, sleep latency, WASO, PLM frequency, and side effects. Participants in the RCTs received dosages of gabapentin starting at 300 or 600 mg with up-titration for symptom relief. Participants had a mean age of 56 years (69% female). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving dosages of 300–2,400 mg for 1 week to 10 months. Meta-analyses were performed to assess the efficacy of gabapentin as a treatment for adults with RLS. The meta-analyses are provided in **Figure S20** through **Figure S35**. A summary of findings table is provided in **Table S2**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of gabapentin to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

Disease severity: The efficacy of gabapentin to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 1 RCT[35] in 44 participants. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −8.40 points (95% CI: −12.0 to −4.8 points) as measured by the IRLS (see **Figure S20**).

The efficacy of gabapentin to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 3 observational studies[38–40] in 33 participants. The duration of patient follow-up after treatment ranged from 2–10 months. The meta-analysis demonstrated a clinically significant reduction in disease severity of −9.77 points (95% CI: −12.35 to −7.2 points) as measured by the IRLS (see **Figure S21**).

The efficacy of gabapentin to reduce disease severity as measured by the CGI-S was evaluated using an analysis of 1 RCT[35] in 44 participants. The duration of patient follow-up after treatment was 6 weeks. The analysis demonstrated a clinically significant decrease in disease severity of −1.1 points (95% CI: −1.93 to −0.27 points) as measured by the CGI-S (see **Figure S22**).

The certainty of evidence for disease severity ranged from moderate to low due to risk of bias associated with observational studies and imprecision.

QOL: The efficacy of gabapentin to improve QOL was evaluated from an analysis of 1 observational study[38] that reported on the RLS-QOL instrument scale in 9 participants. The duration of patient follow-up after treatment was 10 months. The analysis demonstrated a nonclinically significant improvement in QOL of 1.6 points (95% CI: −0.12 to 3.32) as measured by the RLS-QOL instrument scale (see **Figure S23**). The certainty of evidence was very low due to imprecision.

Sleep quality: The efficacy of gabapentin to improve sleep quality was evaluated based on an analysis of 1 RCT[35] in 44 participants that reported on the Pittsburgh Sleep Quality Index (PSQI) scale. The duration of patient follow-up after treatment was 6 weeks. The analysis demonstrated a nonclinically significant improvement in sleep quality of −2.90 points (95% CI: −4.02 to −1.78) as measured by the PSQI scale (see **Figure S24**).

The efficacy of gabapentin to improve sleep quality was evaluated based on an analysis of 2 observational studies[38,40] that reported on the PSQI scale in 25 participants. The duration of patient follow-up after treatment ranged from 2–10 months. The analysis demonstrated a nonclinically significant improvement in sleep quality of −3.73 points (95% CI: −10.68 to 3.22) as measured by the PSQI scale (see **Figure S25**).

The certainty of evidence for sleep quality ranged from low to moderate due to risk of bias associated with observational studies and imprecision.

Adverse effects: A meta-analysis of 2 RCTs[35,36] reported on the total adverse events that led to study withdrawal. There was

a total of 64 participants in the studies. The duration of patient follow-up after treatment was up to 6 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.0 (95% CI: −0.04 to 0.04) with an absolute risk of 0 events/1,000 patients (95% CI: −40 to 40 events/1,000 patients) with use of gabapentin (see **Figure S26**).

A meta-analysis of 4 observational studies[37–40] reported on the total adverse events that led to study withdrawal. There was a total of 50 participants in the studies. The duration of patient follow-up after treatment ranged from 2–10 months. The meta-analysis demonstrated a clinically significant risk difference of 0.06 (95% CI: −0.03 to 0.15) with an absolute risk of 60 events/1,000 patients (95% CI: −30 to 150 events/1,000) with use of gabapentin (see **Figure S27**).

A meta-analysis of 1 RCT[35] reported on the incidence of somnolence. There was a total of 48 participants in the study. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.09 (95% CI: −0.05 to 0.22) with an absolute risk of 90 events/1,000 patients (95% CI: −50 to 220 events/1,000 patients) with use of gabapentin (see **Figure S28**).

A meta-analysis of 3 observational studies[37–39] reported on the incidence of somnolence. There was a total of 26 participants in the studies. The duration of patient follow-up after treatment ranged from 6–10 months. The analysis demonstrated a clinically significant risk difference of 0.16 (95% CI: −0.01 to 0.32) with an absolute risk of 160 events/1,000 patients (95% CI: −10 to 320 events/1,000) with use of gabapentin (see **Figure S29**).

A meta-analysis of 3 observational studies[37–39] that reported on the incidence of dizziness. There was a total of 26 participants in the studies. The duration of patient follow-up after treatment ranged from 6–10 months. The meta-analysis demonstrated a clinically significant risk difference of 0.13 (95% CI: −0.09 to 0.34) with an absolute risk of 130 events/1,000 patients (95% CI: −90 to 340 events/1,000 patients) with use of gabapentin (see **Figure S30**).

Analysis of 1 RCT[35] that reported on the incidence of augmentation. There was a total of 48 participants in the study. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of 0.00 (95% CI: −0.08 to 0.08) with an absolute risk of 0 events/1,000 patients (95% CI: −80 to 80 events/1,000 patients) with use of gabapentin (see **Figure S31**).

The certainty of evidence for unwanted side effects ranged from very low due to risk of bias associated with observational studies and imprecision to high.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of gabapentin: PLM frequency, sleep latency, and WASO.

PLM frequency: The efficacy of gabapentin to decrease PLM frequency was evaluated using a meta-analysis of 2 RCTs.[35,36] There was a total of 64 participants in the studies. The duration of patient follow-up after treatment was up to 6 weeks. The meta-analysis demonstrated a decrease of −9.2 PLMs/h (95% CI: −17.0 to −1.3 PLMs/h) as measured by the PLMI (see **Figure S32**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

The efficacy of gabapentin to decrease PLM frequency was evaluated using a meta-analysis of 2 observational studies.[38,39] There was a total of 17 participants in the studies. The duration of patient follow-up after treatment was 10 months. The meta-analysis demonstrated a decrease of −17.0 PLMs/h (95% CI: −31.8 to −2.3 PLMs/h) as measured by the PLMI (see **Figure S33**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

Sleep latency: The efficacy of gabapentin to decrease sleep latency was evaluated using a meta-analysis of 2 RCTs.[35,36] There was a total of 64 participants in the studies. The duration of patient follow-up after treatment was up to 6 weeks. Meta-analysis demonstrated a nonclinically significant decrease of −8.2 minutes (95% CI: −16.9 to 0.5 minutes) (see **Figure S34**).

WASO: The efficacy of gabapentin to decrease WASO was evaluated using analysis of 1 RCT.[36] There was a total of 80 patients in the study. The duration of patient follow-up after treatment was not reported. Meta-analysis demonstrated a clinically significant decrease in WASO of −60.5 minutes (95% CI: −86.7 to −34.3 minutes) with gabapentin (see **Figure S35**).

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of gabapentin in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S2**).

Benefits vs harms

The potential benefits of gabapentin in adults with RLS include a clinically significant reduction in disease severity and WASO. The potential harms include a clinically significant risk of somnolence and dizziness that may or may not resolve over time. No risk of augmentation was reported. The TF judged that the potential benefits of gabapentin in adults with RLS outweigh the potential harms.

Resource use

The current unit costs for gabapentin ranges from $0.03 for a 100 mg capsule to $0.13 for a 800 mg tablet.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally be accepting of treatment with gabapentin.

Pregabalin

A total of 3 RCTs[41–43] investigated the use of pregabalin in adults with RLS to improve 1 or more of the following

outcomes: disease severity, QOL, sleep quality, WASO, and unwanted side effects. Participants in a dose-finding RCT received 50–450 mg pregabalin while the remaining RCTs participants received 300 mg pregabalin. Participants in the RCTs had a mean age of 54 years (62% female) and were diagnosed with moderate to severe RLS. Meta-analyses were performed to assess the efficacy of pregabalin as a treatment for adults with RLS. The meta-analyses are provided in **Figure S36** through **Figure S42**. A summary of findings table is provided in **Table S3**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of pregabalin to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

Disease severity: The efficacy of pregabalin to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 RCTs[41,42] in a total of 486 participants. The duration of patient follow-up after treatment ranged from 6–52 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −4.8 points (95% CI: −6.2 to −3.4 points) as measured by the IRLS (see **Figure S36**). The certainty of evidence for disease severity was high.

QOL: The efficacy of pregabalin to improve QOL was evaluated from an analysis of 1 RCT[42] that reported on the RLS-QOL Abetz scale in a total of 349 participants. The duration of patient follow-up after treatment was 52 weeks. The analysis demonstrated a nonclinically significant improvement in QOL of 4.6 points (95% CI: 2.0–7.2 points) as measured by the RLS-QOL Abetz scale (see **Figure S37**). The certainty of evidence was moderate due to imprecision.

Sleep quality: The efficacy of pregabalin to improve sleep quality was evaluated based on an analysis of 2 RCTs[41,43] that reported on the MOSS scale in a total of 282 participants. The duration of patient follow-up after treatment ranged from 4–6 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of 0.4 points (95% CI: 0.1–0.7 points) as measured by the MOSS scale (see **Figure S38**). The certainty of evidence for sleep quality was moderate due to imprecision.

Adverse effects: A meta-analysis of 3 RCTs[41–43] reported on the total adverse events that led to study withdrawal in a total of 585 participants. The duration of patient follow-up after treatment ranged from 4–52 weeks. The meta-analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.12 (95% CI: −0.04 to 0.29) with an absolute risk of 120 events/1,000 patients (95% CI: −40 to 290 events/1,000 patients) with use of pregabalin (see **Figure S39**).

A meta-analysis of 3 RCTs[41–43] reported dizziness as a side effect in a total of 705 participants. The duration of patient follow-up after treatment ranged from 4–52 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.18 (95% CI: 0.12–0.25) with an absolute risk of 180 events/1,000 patients (95% CI: 120–250 events/1,000 patients) with use of pregabalin (see **Figure S40**).

A meta-analysis of 3 RCTs[41–43] also reported somnolence in a total of 646 participants. The duration of patient follow-up after treatment ranged from 4–52 weeks. The analysis demonstrated a clinically significant risk difference of 0.17 (95% CI: 0.10–0.23) with an absolute risk of 170 events/1,000 patients (95% CI: 100–230 events/1,000) with use of pregabalin (see **Figure S41**).

The certainty of evidence for adverse effects ranged from high to moderate due to imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of pregabalin: WASO.

WASO: The efficacy of pregabalin to decrease WASO was evaluated using a meta-analysis of 1 RCT[43] in a total of 145 participants. The duration of patient follow-up after treatment was 4 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of −27.1 minutes (95% CI: −38.7 to −15.5 minutes) with pregabalin (see **Figure S42**). The certainty of evidence for WASO was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of pregabalin in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S3**).

Benefits vs harms

The potential benefits of pregabalin in adults with RLS include a clinically significant improvement in disease severity, sleep quality, and WASO. The potential harms include a clinically significant risk of somnolence and dizziness that may or may not resolve over time. Other side effects including weight gain, peripheral edema, fatigue, and vertigo have been reported.[44] The TF judged that the potential benefits of pregabalin in adults with RLS outweigh the potential harms.

Resource use

The current unit costs for pregabalin ranges from $0.04 for a 25 mg capsule to $0.09 for a 300 mg capsule.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally be accepting of treatment with pregabalin.

Intravenous (IV) ferric carboxymaltose

A total of 5 RCTs[45–48] investigated the use of IV ferric carboxymaltose in adults with RLS to improve 1 or more of the following outcomes: disease severity, QOL, sleep quality, and adverse effects. Participants in the RCTs received 500–1,500 mg of

IV ferric carboxymaltose and had a mean age of 52 years (79% female). Meta-analyses were performed to assess the efficacy of IV ferric carboxymaltose as a treatment for adults with RLS. The meta-analyses are provided in **Figure S43** through **Figure S48**. A summary of findings table is provided in **Table S4**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV ferric carboxymaltose to treat adults with RLS: disease severity, QOL, sleep quality, and adverse effects.

Disease severity: The efficacy of IV ferric carboxymaltose to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 5 RCTs[45–49] in a total of 237 participants. The duration of patient follow-up after treatment ranged from 4–52 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −7.4 points (95% CI: −11.9 to −2.9 points) as measured by the IRLS (see **Figure S43**).

The efficacy of IV ferric carboxymaltose to reduce disease severity as measured by the CGI-I was evaluated using a meta-analysis of 2 RCTs[45,48] in a total of 53 participants. The duration of patient follow-up after treatment ranged from 4–24 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 30% (95% CI: 16–44%) as measured by the CGI-I (see **Figure S44**).

The efficacy of IV ferric carboxymaltose to reduce disease severity as measured by the PGI was evaluated using a meta-analysis of 1 RCT[45] in a total of 40 participants. The duration of patient follow-up after treatment was 24 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 37% (95% CI: 12–63%) as measured by the PGI (see **Figure S45**). The certainty of evidence for disease severity ranged from moderate due to imprecision to high.

The certainty of evidence for disease severity ranged from moderate to high due to imprecision.

QOL: The efficacy of IV ferric carboxymaltose to improve QOL was evaluated from an analysis of 3 RCTs[45–47] that reported on the RLS-QOL Abetz scale in a total of 136 participants. The duration of patient follow-up after treatment ranged from 6–52 weeks. The analysis demonstrated a clinically significant improvement in QOL of 11.1 points (95% CI: −0.3 to 22.5 points) as measured by the RLS-QOL Abetz scale (see **Figure S46**). The certainty of evidence was moderate due to imprecision.

Sleep quality: The efficacy of IV ferric carboxymaltose to improve sleep quality was evaluated based on an analysis of 3 RCTs[46,47,49] that reported on the PSQI scale in a total of 111 participants. The duration of patient follow-up after treatment ranged from 6–52 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of −4.2 points (95% CI: −8.8 to 0.3 points) as measured by the PSQI scale (see **Figure S47**). The certainty of evidence for sleep quality was very low due to imprecision and inconsistency.

Adverse effects: A meta-analysis of 4 RCTs[45–48] reported on the total adverse events that led to study withdrawal in a total of 248 participants. The duration of patient follow-up after treatment ranged from 4–52 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: −0.03 to 0.03) with an absolute risk of 0 events/1,000 patients (95% CI: −30 to 30 events/1,000 patients) with use of IV ferric carboxymaltose (see **Figure S48**). The certainty of evidence for unwanted side effects was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV ferric carboxymaltose in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S4**).

Benefits vs harms

The potential benefits of IV ferric carboxymaltose in adults with RLS include a clinically significant improvement in disease severity and QOL. The potential harms include a nonclinically significant risk of dizziness that may or may not resolve over time. The TF judged that the potential benefits of IV ferric carboxymaltose in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs for IV ferric carboxymaltose to be moderate due to cost of infusion at a treatment center.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally be accepting of treatment with IV ferric carboxymaltose.

IV low molecular weight (LMW) iron dextran

One observational study[50] investigated the use of IV LMW iron dextran in adults with RLS to improve 1 or more of the following outcomes: disease severity and unwanted side effects. Participants in the observational study received 1,000 mg of IV LMW iron dextran and had a mean age of 55 years (72% female). Analyses were performed to assess the efficacy of IV LMW iron dextran as a treatment for adults with RLS. The analyses is provided in **Figure S49** through **Figure S50**. A summary of findings table is provided in **Table S5**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV LMW iron dextran to treat adults with RLS: disease severity and adverse events.

Disease severity: The efficacy of IV LMW iron dextran to reduce disease severity as measured by the IRLS was reported in 1 observational study[50] in a total of 23 participants. The duration of patient follow-up after treatment was 3 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −6.8 points (95% CI: −11.5 to −2.1 points) as measured by the IRLS (see **Figure S49**). The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

Adverse effects: A meta-analysis of 3 observational studies[50–52] reported on the total adverse events that led to study withdrawal in a total of 59 participants. The duration of patient follow-up after treatment ranged from 2–60 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.03 (95% CI: −0.04 to 0.09) with use of IV LMW iron dextran (see **Figure S50**). The certainty of evidence for unwanted side effects was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV LMW iron dextran in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S5**).

Benefits vs harms

The potential benefits of IV LMW iron dextran in adults with RLS include a clinically significant improvement in disease severity. The potential harms include a nonclinically significant risk of adverse events that lead to study withdrawal. The TF judged that the potential benefits of IV LMW iron dextran in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs for IV LMW iron dextran to be moderate due to cost of infusion at a treatment center.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally be accepting of treatment with IV LMW iron dextran.

IV ferumoxytol

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV iron ferumoxytol to treat adults with RLS: disease severity and adverse events.

Disease severity: The efficacy of IV ferumoxytol to reduce disease severity as measured by the IRLS was reported in 1 RCT[53] in a total of 48 participants. The RCT study compared IV ferumoxytol to another treatment and prepost data were used as there was no placebo arm. The RCT demonstrated clinically significant improvement in disease severity. The duration of patient follow-up after treatment was 6 weeks. The results demonstrated a clinically significant reduction in disease severity of −7.9 points (95% CI: −11.7 to −4.0 points) as measured by the IRLS (see **Figure S51**). The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

Adverse effects: One RCT[53] reported on the total adverse events that did not lead to study withdrawal in any of the 48 participants. The duration of patient follow-up after treatment was 6 weeks. The certainty of evidence for unwanted side effects was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV ferumoxytol in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S6**).

Benefits vs harms

The potential benefits of IV ferumoxytol in adults with RLS include a clinically significant improvement in disease severity. The potential harms included a nonclinically significant risk of adverse events that did not lead to study withdrawal. The TF judged that the potential benefits of IV iron ferumoxytol in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs for IV ferumoxytol to be moderate due to cost of infusion at a treatment center.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally be accepting of treatment with IV ferumoxytol.

Ferrous sulfate

A total of 2 RCTs[54,55] investigated the use of ferrous sulfate in adults with RLS and an iron deficiency to improve 1 or more of the following outcomes: disease severity and unwanted side effects. Participants in the RCTs received 325 mg ferrous sulfate, once or twice daily, and had a mean age of 59 years (65% female). Meta-analyses were performed to assess the efficacy of oral iron as a treatment for adults with RLS and iron deficiency. The meta-analyses are provided in **Figure S52** and **Figure S53**. A summary of findings table is provided in **Table S7**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of oral iron to treat adults with

RLS and an iron deficiency: disease severity and unwanted side effects.

Disease severity: The efficacy of oral iron to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 1 RCT[55] in a total of 18 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −9.2 points (95% CI: −15.2 to −3.2 points) as measured by the IRLS (see **Figure S52**). The certainty of evidence for disease severity was moderate due to imprecision.

Unwanted side effects: A meta-analysis of 2 RCTs[54,55] reported on the total adverse events that led to study withdrawal in a total of 46 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.10 (95% CI: −0.12 to 0.32) with an absolute risk of 100 events/1,000 patients (95% CI: −120 to 320 events/1,000 patients) with use of ferrous sulfate (see **Figure S53**). The certainty of evidence for disease severity was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of ferrous sulfate in adults with RLS and an iron deficiency was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S7**).

Benefits vs harms

The potential benefits of ferrous sulfate in adults with RLS and an iron deficiency include a clinically significant reduction in disease severity. The TF judged that the potential benefits of ferrous sulfate in adults with RLS and iron deficiency outweigh the potential harms.

Resource use

The TF judged the costs of ferrous sulfate are negligible.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS and iron deficiency would generally be accepting of treatment with ferrous sulfate.

Dipyridamole

A total of 1 RCT[56] and 1 observational study[57] investigated the use of dipyridamole in adults with RLS to improve 1 or more of the following outcomes: disease severity, sleep latency, WASO, and unwanted side effects. Participants in the RCT received dosages of dipyridamole starting at 100 mg with up-titration to 300 mg if clinically necessary. Participants had a mean age of 60 years (65% female). The observational study was a before-and-after treatment design with participants serving as their own controls and receiving dosages starting at 100 mg with up-titration to 400 mg if clinically necessary. Meta-analyses were performed to assess the efficacy of dipyridamole as a treatment for adults with RLS. The meta-analyses are provided in **Figure S54** through **Figure S59**. A summary of findings table is provided in **Table S8**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of dipyridamole to treat adults with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of dipyridamole to reduce disease severity as measured by the IRLS was reported in 1 RCT[56] in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant reduction in disease severity of −7.6 points (95% CI: −9.1 to −6.1 points) as measured by the IRLS (see **Figure S54**). The certainty of evidence was moderate due to imprecision.

Unwanted side effects: One RCT[56] reported on the total adverse events that led to study withdrawal in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: −0.07 to 0.07) with an absolute risk of 0 events/1,000 patients (95% CI: −70 to 70 events/1,000 patients) with use of dipyridamole (see **Figure S55**).

One RCT[56] reported on the incidence of dizziness in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant risk ratio of 1.5 (95% CI: 0.3–8.3) with an absolute risk of 35 events/1,000 patients (95% CI: −52 to 521 events/1,000 patients) with use of dipyridamole (see **Figure S56**).

One observational study[57] reported on the incidence of dizziness in a total of 15 participants. The duration of patient follow-up after treatment was 2 months. The analysis demonstrated a clinically significant risk difference of 0.13 (95% CI: −0.06 to 0.33) with an absolute risk of 130 events/1,000 patients (95% CI: −60 to 330 events/1,000 patients) with use of dipyridamole (see **Figure S57**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of dipyridamole: sleep latency and WASO.

Sleep latency: The efficacy of dipyridamole to decrease sleep latency was reported in 1 RCT[56] in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. Meta-analysis demonstrated a nonclinically significant decrease of −7.2 minutes (95% CI: −12.3 to −2.1 minutes) (see **Figure S58**). The certainty of evidence was moderate due to imprecision.

WASO: The efficacy of dipyridamole to decrease WASO was reported in 1 RCT[56] in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. Meta-analysis

demonstrated a clinically significant decrease in WASO of −14.5 minutes (95% CI: −28.6 to −0.4 minutes) with dipyridamole (see **Figure S59**). The certainty of evidence for WASO was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of dipyridamole in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S8**).

Benefits vs harms

The potential benefits of dipyridamole in adults with RLS include a clinically significant reduction in disease severity and WASO. The potential harms include a clinically significant risk of dizziness that may or may not resolve over time. The TF judged that the potential benefits of dipyridamole in adults with RLS outweigh the potential harms.

Resource use

The current unit costs for dipyridamole ranges from $0.19 for a 50 mg tablet to $0.67 for a 75 mg tablet.[27,34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally be accepting of treatment with dipyridamole.

Extended-release (ER) oxycodone and other opioids

A total of 2 RCTs[58,59] investigated the use of oxycodone in adults with RLS to improve 1 or more of the following outcomes: disease severity, sleep quality, sleep latency, and unwanted side effects, either ER oxycodone-naloxone or oxycodone immediate release. Participants in the RCTs received dosages of oxycodone ER starting at 5 mg with up-titration to 40 mg if clinically necessary. Participants had a mean age of 62 years (66% female). Meta-analyses were performed to assess the efficacy of oxycodone as a treatment for adults with RLS. The meta-analyses are provided in **Figure S60** through **Figure S67**. A summary of findings table is provided in **Table S9**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of oxycodone to treat adults with RLS: disease severity, sleep quality, and unwanted side effects.

Disease severity: The efficacy of oxycodone ER to reduce disease severity as measured by the IRLS was evaluated in 1 RCT[58] in a total of 276 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a clinically significant reduction in disease severity of −5.6 points (95% CI: −8.2 to −3.0 points) as measured by the IRLS (see **Figure S60**). The certainty of evidence for disease severity was high.

Sleep quality: The efficacy of oxycodone ER to improve sleep quality was evaluated in 1 RCT[58] that reported on the MOSS scale in a total of 276 participants. The duration of patient follow-up after treatment was 12 weeks. The results for sleep quality were 0.14 points (95% CI: −0.10 to 0.37 points) as measured by the MOSS scale which did not show a clinically significant improvement (see **Figure S61**). The certainty of evidence for sleep quality was moderate due to imprecision.

Adverse effects: A meta-analysis of 2 RCTs[58,59] reported on the total adverse events that led to study withdrawal in a total of 326 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. The meta-analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.06 (95% CI: −0.00 to 0.12) with an absolute risk of 60 events/1,000 patients (95% CI: −0 to 120 events/1,000 patients) with use of oxycodone (see **Figure S62**).

One RCT[58] reported on the incidence of fatigue in a total of 304 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 2.3 (95% CI: 1.4–3.6) with an absolute risk of 169 events/1,000 patients (95% CI: 52–338 events/1,000 patients) with use of oxycodone (see **Figure S63**).

One RCT[58] reported on the incidence of somnolence in a total of 304 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 2.4 (95% CI: 1.0–5.5) with an absolute risk of 64 events/1,000 patients (95% CI: 0–205 events/1,000 patients) with use of oxycodone (see **Figure S64**).

One RCT[58] reported on the incidence of dizziness in a total of 304 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 3.3 (95% CI: 1.1–10.0) with an absolute risk of 60 events/1,000 patients (95% CI: 3–234 events/1,000 patients) with use of oxycodone (see **Figure S65**).

The certainty of evidence for unwanted side effects was moderate due to imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of oxycodone: PLM frequency and sleep latency.

PLM frequency: The efficacy of oxycodone to decrease PLM frequency was reported in 1 RCT[59] in a total of 11 patients. The duration of patient follow-up after treatment was 2 weeks. The meta-analysis demonstrated a decrease of −34.5 PLMs/h (95% CI: −62.7 to −6.4 PLMs/h) as measured by the PLMI (see **Figure S66**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

Sleep latency: The efficacy of oxycodone to decrease sleep latency was evaluated reported in 1 RCT[59] in a total of 11 patients. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant

decrease of −25.5 minutes (95% CI: −68.4 to 17.4 minutes) (see **Figure S67**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of oxycodone in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S9**).

Benefits vs harms

The potential benefits of oxycodone in adults with RLS include a clinically significant reduction in disease severity and sleep latency. The potential harms include a clinically significant risk of fatigue, somnolence and dizziness that may or may not resolve over time. No risk of augmentation was reported. The TF judged that the potential benefits of oxycodone in adults with RLS outweigh the potential harms, despite the potential risk of abuse, dependence, or overdose.

Resource use

The current unit costs for oxycodone ranges from $0.07 for a 5 mg tablet to $18.12 for a 36 mg tablet.[34] The TF judged that the costs of oxycodone and other opioids vary depending on formulation.

Patient values and preferences

The TF judged that there is important uncertainty or variability in how much patients value the main outcomes. The TF judged that there would be variability among adults with RLS regarding the long-term use of oxycodone and other opioids. These variabilities are due to the potential risks of abuse, dependence, and death in the event of a significant overdose of oxycodone and other opioids.

Bilateral high-frequency peroneal nerve stimulation

Two RCTs[60,61] investigated the use of bilateral high-frequency peroneal nerve stimulation in adults with RLS to improve 1 or more of the following outcomes: disease severity. Participants in the RCTs utilized a self-administered stimulation session for 30 minutes at bedtime. Participants had a mean age of 57 years (57% female). Meta-analyses were performed to assess the efficacy of peroneal nerve stimulation as a treatment for adults with RLS. The meta-analyses are provided in **Figure S68** and **Figure S69**. A summary of findings table is provided in **Table S10**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of bilateral high-frequency peroneal nerve stimulation to treat adults with RLS: disease severity.

Disease severity: The efficacy of peroneal nerve stimulation to reduce disease severity as measured by the IRLS was reported 2 RCTs[60,61] in a total of 205 participants. The duration of patient follow-up after treatment ranged from 2–4 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −3.4 points (95% CI: −5.0 to −1.8 points) as measured by the IRLS (see **Figure S68**).

The efficacy of peroneal nerve stimulation to reduce disease severity as measured by the CGI-I was evaluated using a meta-analysis of 2 RCTs[60,61] in a total of 191 participants. The duration of patient follow-up after treatment ranged from 2–4 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 34% (95% CI: 21–46%) as measured by the CGI-I (see **Figure S69**).

The certainty of evidence for disease severity was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of bilateral high-frequency peroneal nerve stimulation in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to risk of bias (see **Table S10**).

Benefits vs harms

The potential benefits of bilateral high-frequency peroneal nerve stimulation in adults with RLS include a clinically significant reduction in disease severity. Side effects including uncomfortable sensations, skin irritation, muscle fatigue, upper respiratory infection, gastrointestinal distress, and flu have been reported. The TF judged that the potential benefits of peroneal nerve stimulation in adults with RLS outweigh the potential harms.

Resource use

The current unit cost for the bilateral high-frequency peroneal nerve stimulation device is $7,500.[34,62] The TF judged these costs are high.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally be accepting of treatment with peroneal nerve stimulation.

Levodopa

A total of 3 RCTs[63–65] and 7 observational studies[66–72] investigated the use of levodopa in adults with RLS to improve 1 or more of the following outcomes: disease severity, QOL, sleep quality, WASO, and unwanted side effects. Participants in the RCTs received 100–200 mg of levodopa (with peripheral decarboxylase inhibitor carbidopa or benserazide). Participants had a mean age of 55 years (51% female). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving 100–500 mg of levodopa (with peripheral decarboxylase inhibitor carbidopa or benserazide). Meta-analyses were performed to assess the efficacy of levodopa as a treatment for adults with RLS. The meta-analyses are provided in **Figure S70** through **Figure S78**.

A summary of findings table is provided in **Table S11**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of levodopa to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

Disease severity: The efficacy of levodopa to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 observational studies[67,70] in a total of 81 participants. The duration of patient follow-up after treatment ranged from 3 days to 4 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −4.7 points (95% CI: −7.0 to −2.4 points) as measured by the IRLS (see **Figure S70**).

The efficacy of levodopa to reduce disease severity as measured by the CGI-S was reported in 1 RCT[65] in a total of 34 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a nonclinically significant improvement of −0.2 (95% CI: −0.8 to 0.4) as measured by the CGI-S (see **Figure S71**).

The certainty of evidence for disease severity ranged from very low to low due to risk of bias associated with observational studies and imprecision.

QOL: The efficacy of levodopa to improve QOL was evaluated from an analysis of 1 observational study[70] that reported on the RLS-QOL instrument scale in a total of 18 participants. The duration of patient follow-up after treatment was 3 days. The analysis demonstrated a nonclinically significant improvement in QOL of 0.1 points (95% CI: −0.7 to 0.9 points) as measured by the RLS-QOL instrument scale (see **Figure S72**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Sleep quality: The efficacy of levodopa to improve sleep quality was evaluated based on an analysis of 1 observational study[70] that reported on the PSQI scale in a total of 18 participants. The duration of patient follow-up after treatment was 3 days. The analysis demonstrated a clinically significant improvement in sleep quality of −3.2 points (95% CI: −6.3 to −0.1) as measured by the PSQI scale (see **Figure S73**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Adverse effects: A meta-analysis of 3 RCTs[63–65] reported on the total adverse events that led to study withdrawal in a total of 138 participants. The duration of patient follow-up after treatment ranged from 4 weeks to 18 months. The meta-analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of −0.02 (95% CI: −0.08 to 0.04) with an absolute risk of −20 events/1,000 patients (95% CI: −80 to 40 events/1,000 patients) with use of levodopa (see **Figure S74**).

A meta-analysis of 2 RCTs[63,64] reported on the incidence of augmentation in a total of 104 participants. The duration of patient follow-up after treatment ranged from 4 weeks to 18 months. The meta-analysis demonstrated a clinically significant risk difference of 0.11 (95% CI: −0.03 to 0.25) with an absolute risk of 115 events/1,000 patients (95% CI: 29–202 events/1,000 patients) with use of levodopa (see **Figure S75**).

A meta-analysis of 7 observational studies[66–72] reported on the incidence of augmentation in a total of 416 participants. The duration of patient follow-up after treatment ranged from 3 days to 12 months. The meta-analysis demonstrated a clinically significant risk difference of 0.39 (95% CI: 0.17–0.61) with an absolute risk of 310 events/1,000 patients (95% CI: 266–355 events/1,000 patients) with use of levodopa (see **Figure S76**).

A meta-analysis of 2 observational studies[67,71] reported on the incidence of dizziness/vertigo in a total of 246 participants. The duration of patient follow-up after treatment ranged from 4–30 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.11 (95% CI: 0.00–0.22) with an absolute risk of 110 events/1,000 patients (95% CI: 0–220 events/1,000 patients) with use of levodopa (see **Figure S77**).

One observational study[64] reported on the incidence of somnolence in a total of 40 participants. The duration of patient follow-up after treatment was 18 months. The meta-analysis demonstrated a clinically significant risk difference of 0.05 (95% CI: −0.18 to 0.28) with an absolute risk of 50 events/1,000 patients (95% CI: −180 to 280 events/1,000 patients) with use of levodopa (see **Figure S78**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of levodopa in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S11**).

Benefits vs harms

The potential benefits of levodopa in adults with RLS show improvements in disease severity and sleep quality that did not meet clinical significance. The potential harms include a clinically significant risk of somnolence, dizziness/vertigo, and augmentation that may or may not resolve over time. The TF judged that the potential harms of levodopa in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for levodopa was $0.07 for a 25/100 mg tablet.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant risk of harms, the TF judged that most adults with RLS would generally not be accepting treatment with levodopa.

Pramipexole

A total of 17 RCTs[41,43,73–87] and 7 observational studies[67,75,88–92] investigated the use of pramipexole in adults with RLS to improve 1 or more of the following outcomes: disease severity, QOL, sleep quality, and unwanted side effects. Participants in the RCTs had a mean age of 55 years (65% female) and were diagnosed with moderate to severe RLS. Most participants received dosages of pramipexole from 0.125–0.75 mg, with a single study allowing up to 1.5 mg. Five observational studies were before-and-after treatment design (including long-term follow up), with participants serving as their own controls. Two observational studies were retrospective records reviews. Meta-analyses were performed to assess the efficacy of pramipexole as a treatment for adults with RLS. The meta-analyses are provided in **Figure S79** through **Figure S87**. A summary of findings table is provided in **Table S12**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of pramipexole to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

Disease severity: The efficacy of pramipexole to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 10 RCTs[42,73–75,77,82,84–87] in a total of 2,917 participants. The duration of patient follow-up after treatment ranged from 3–52 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −4.9 points (95% CI: −6.2 to −3.5 points) as measured by the IRLS (see **Figure S79**). The certainty of evidence was high.

QOL: The efficacy of pramipexole to improve QOL was evaluated from an analysis of 4 RCTs[42,73,82,86] that reported on the RLS-QOL Abetz scale in a total of 1,634 participants. The duration of patient follow-up after treatment ranged from 12–52 weeks. The analysis demonstrated a clinically significant improvement in QOL of 5.4 points (95% CI: 2.1–8.7 points) as measured by the RLS-QOL Abetz scale (see **Figure S80**). The certainty of evidence was moderate due to inconsistency.

Sleep quality: The efficacy of pramipexole to improve sleep quality was evaluated based on an analysis of 2 RCTs[73,93] that reported on the PSQI and MOSS scales in a total of 397 participants. The duration of patient follow-up after treatment ranged from 12–52 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of 0.7 (95% CI: −0.1 to 1.5) as measured by the PSQI and MOSS scales (see **Figure S81**). The certainty of evidence was moderate due to imprecision.

Adverse effects: A meta-analysis of 17 RCTs[41,43,73–87] reported on the total adverse events that led to study withdrawal in a total of 3,548 participants. The duration of patient follow-up after treatment ranged from 3–52 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.02 (95% CI: −0.02 to 0.06) with an absolute risk of 20 events/1,000 patients (95% CI: −20 to 60 events/1,000 patients) with use of pramipexole (see **Figure S82**).

A meta-analysis of 2 RCTs[42,74] reported on the incidence of augmentation in a total of 825 participants. The duration of patient follow-up after treatment ranged from 26–52 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.09 (95% CI: 0.04–0.14) with an absolute risk of 90 events/1,000 patients (95% CI: 40–140 events/1,000 patients) with use of pramipexole (see **Figure S83**).

A meta-analysis of 7 observational studies[67,75,88–92] reported on the incidence of augmentation in a total of 640 participants. The duration of patient follow-up after treatment ranged from 4 weeks to 12 years. The meta-analysis demonstrated a clinically significant risk difference of 0.18 (95% CI: 0.08–0.27) with an absolute risk of 180 events/1,000 patients (95% CI: 80–270 events/1,000 patients) with use of pramipexole (see **Figure S84**).

A meta-analysis of 7 RCTs[42,74,75,77,84–86] reported on the incidence of somnolence in a total of 1,998 participants. The duration of patient follow-up after treatment ranged from 6 weeks to 52 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of 0.04 (95% CI: 0.01–0.06) with an absolute risk of 40 events/1,000 patients (95% CI: 10–60 events/1,000 patients) with use of pramipexole (see **Figure S85**).

A meta-analysis of 6 RCTs[42,77,83,84,86,87] reported on the incidence of dizziness in a total of 1,745 participants. The duration of patient follow-up after treatment ranged from 6 weeks to 52 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of 0.04 (95% CI: 0.00–0.09) with an absolute risk of 40 events/1,000 patients (95% CI: 0–90 events/1,000 patients) with use of pramipexole (see **Figure S86**).

One observational study[89] reported on the incidence of impulse control disorders in a total of 50 participants. The duration of patient follow-up after treatment ranged from 6 months to 12 years. The meta-analysis demonstrated a clinically significant risk difference of 0.10 (95% CI: 0.01–0.19) with an absolute risk of 100 events/1,000 patients (95% CI: 10–190 events/1,000 patients) with use of pramipexole (see **Figure S87**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies, imprecision, and inconsistency.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of pramipexole in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies, imprecision, and inconsistency (see **Table S12**).

Benefits vs harms

The potential benefits of pramipexole in adults with RLS include a clinically significant improvement in disease severity, QOL, and sleep quality. The potential harms include a clinically significant risk of somnolence, dizziness, impulse control disorders, and augmentation that may or may not resolve over time.

The TF judged that the balance of potential harms in adults with RLS outweighs the benefits.

Resource use

The current unit costs for pramipexole ranges from $0.04 for a 0.125 mg tablet to $0.08 for a 1.5 mg tablet.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant risks, the TF judged that most adults with RLS would generally not be accepting of treatment with pramipexole.

Transdermal rotigotine

A total of 8 RCTs[24,94–100] and 3 observational studies[24,99,101] investigated the use of transdermal rotigotine in adults with RLS to improve 1 or more of the following outcomes: disease severity, QOL, sleep quality, and unwanted side effects. Participants in the RCTs had a mean age of 55 years (63% female) and were diagnosed with moderate to severe RLS. Participants received dosages of transdermal rotigotine from 0.5–4.5 mg. All observational studies were before-and-after treatment design with participants diagnosed with moderate to severe RLS and serving as their own controls. Meta-analyses were performed to assess the efficacy of rotigotine as a treatment for adults with RLS. The meta-analyses are provided in **Figure S88** through **Figure S95**. A summary of findings table is provided in **Table S13**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of transdermal rotigotine to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

Disease severity: The efficacy of rotigotine to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 8 RCTs[24,94–100] in a total of 1,905 participants. The duration of patient follow-up after treatment ranged from 1 week to 6 months. The meta-analysis demonstrated a clinically significant reduction in disease severity of −4.7 points (95% CI: −6.2 to −3.2 points) as measured by the IRLS (see **Figure S88**). The certainty of evidence was high.

QOL: The efficacy of rotigotine to improve QOL was evaluated from an analysis of 4 RCTs[96–98,102] that reported on the RLS-QOL Kohnen scale in a total of 1,310 participants. The duration of patient follow-up after treatment ranged from 10 weeks to 6 months. The analysis demonstrated a clinically significant improvement in QOL of −4.5 points (95% CI: −8.2 to −0.9 points) as measured by the RLS-QOL Kohnen scale (see **Figure S89**). The certainty of evidence was moderate due to imprecision.

Sleep quality: The efficacy of rotigotine to improve sleep quality was evaluated based on an analysis of 4 RCTs[24,96,98,103] that reported on the PSQI and MOSS scales in a total of 995 participants. The duration of patient follow-up after treatment ranged from 3–6 months. The meta-analysis demonstrated a clinically significant improvement in sleep quality of 0.2 (95% CI: 0.06–0.34) as measured by the PSQI and MOSS scales (see **Figure S90**). The certainty of evidence was moderate due to imprecision.

Adverse effects: A meta-analysis of 8 RCTs[24,94–100] reported on the total adverse events that led to study withdrawal in a total of 1,927 participants. The duration of patient follow-up after treatment ranged from 1 week to 6 months. The meta-analysis demonstrated a clinically significant risk ratio of adverse events leading to study withdrawal of 1.7 (95% CI: 0.8–3.7) with an absolute risk of 30 events/1,000 patients (95% CI: −8 to 115 events/1,000 patients) with use of rotigotine (see **Figure S91**).

A meta-analysis of 3 RCTs[24,96,98] reported on the incidence of somnolence in a total of 855 participants. The duration of patient follow-up after treatment ranged from 3–6 months. The meta-analysis demonstrated a clinically significant risk ratio of somnolence of 2.3 (95% CI: 1.0–5.3) with an absolute risk of 60 events/1,000 patients (95% CI: 0–199 events/1,000 patients) with use of rotigotine (see **Figure S92**).

A meta-analysis of 4 RCTs[96–98,102] reported on the incidence of dizziness/vertigo in a total of 1,369 participants. The duration of patient follow-up after treatment ranged from 3–6 months. The meta-analysis demonstrated a clinically significant risk ratio of somnolence of 1.0 (95% CI: 0.6–1.9) with an absolute risk of 0 events/1,000 patients (95% CI: −18 to 35 events/1,000 patients) with use of rotigotine (see **Figure S93**).

A meta-analysis of 5 RCTs[97–99,102,104] reported on the incidence of application site reaction in a total of 1,205 participants. The duration of patient follow-up after treatment ranged from 1 week to 6 months. The meta-analysis demonstrated a clinically significant risk ratio of 5.2 (95% CI: 1.4–19.4) with an absolute risk of 210 events/1,000 patients (95% CI: 20 to 920 events/1,000 patients) with use of rotigotine (see **Figure S94**).

A meta-analysis of 3 observational studies[24,99,101] reported on the incidence of augmentation in a total of 1,164 participants. The duration of patient follow-up after treatment ranged from 12 weeks to 5 years. The meta-analysis demonstrated a clinically significant risk difference of 0.06 (95% CI: −0.05 to 0.17) with an absolute risk of 60 events/1,000 patients (95% CI: 050–170 events/1,000 patients) with use of rotigotine (see **Figure S95**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies, imprecision, and inconsistency.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of transdermal rotigotine in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies, imprecision, and inconsistency (see **Table S13**).

Benefits vs harms

The potential benefits of transdermal rotigotine in adults with RLS include a clinically significant improvement in disease

severity, QOL, and sleep quality. The potential harms include a clinically significant risk of somnolence, dizziness/vertigo, augmentation, and application site reaction that may or may not resolve over time. Other side effects including nausea, headache, and asthenia have been reported.[105] Although rates of augmentation reported in the clinical trials was low, study duration may have led to an underestimation of its occurrence. Taking into account the class effect of harms associated with this group, the TF judged that the harms outweigh the benefits.

Resource use

The current unit costs of transdermal rotigotine ranges from $22.66 for a 4 mg/24 hours patch to $22.88 for a 8 mg/24 hours patch.[34] The TF judged these costs are high.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant risks, the TF judged that most adults with RLS would generally not be accepting of treatment with transdermal rotigotine.

Ropinirole

A total of 12 RCTs[106–116] and 2 observational studies[112,117] investigated the use of ropinirole in adults with RLS to improve 1 or more of the following outcomes: disease severity and unwanted side effects. Participants in the RCTs had a mean age of 55 years (62% female) and were diagnosed with moderate to severe RLS. Participants received flexible dosages of ropinirole from 0.25–6 mg. All observational studies were before-and-after treatment design with participants diagnosed with moderate to severe RLS and serving as their own controls. Meta-analyses were performed to assess the efficacy of ropinirole as a treatment for adults with RLS. The meta-analyses are provided in **Figure S96** through **Figure S104**. A summary of findings table is provided in **Table S14**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of ropinirole to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

Disease severity: The efficacy of ropinirole to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 7 RCTs[106,108–111,115,116] in a total of 1,314 participants. The duration of patient follow-up after treatment ranged from 2–26 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −4.0 points (95% CI: −5.4 to −2.6 points) as measured by the IRLS (see **Figure S96**). The certainty of evidence was moderate due to imprecision.

QOL: The efficacy of ropinirole to improve QOL was evaluated from an analysis of 3 RCTs[110,112,116] that reported on the RLS-QOL scale in a total of 768 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a nonclinically significant improvement in QOL of 3.8 points (95% CI: 1.8–5.8 points) as measured by the RLS-QOL scale (see **Figure S97**). The certainty of evidence was moderate due to imprecision.

Sleep quality: The efficacy of ropinirole to improve sleep quality was evaluated based on an analysis of 3 RCTs[107,110,112] that reported on the MOSS scale in a total of 615 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a nonclinically significant improvement in sleep quality of 0.17 points (95% CI: −0.00 to 0.35 points) as measured by the MOSS scale (see **Figure S98**). The certainty of evidence for sleep quality was moderate due to imprecision.

Adverse effects: A meta-analysis of 8 RCTs[36,107,108,110,112,113,115,116,118] reported on the total adverse events that led to study withdrawal in a total of 2,067 participants. The duration of patient follow-up after treatment ranged from 3 days to 12 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.03 (95% CI: −0.01 to 0.06) with an absolute risk of 30 events/1,000 patients (95% CI: −10 to 60 events/1,000 patients) with use of ropinirole (see **Figure S99**).

A meta-analysis of 3 RCTs[110,112,115] reported on the incidence of augmentation in a total of 1,072 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.02 (95% CI: −0.01 to 0.04) with an absolute risk of 20 events/1,000 patients (95% CI: −10 to 40 events/1,000 patients) with use of ropinirole (see **Figure S100**).

One observational study[112] reported on the incidence of augmentation in a total of 269 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.03 (95% CI: −0.01 to 0.05) with an absolute risk of 30 events/1,000 patients (95% CI: 10–50 events/1,000 patients) with use of ropinirole (see **Figure S101**).

One observational study[45] reported on the definite/highly suggestive likelihood of augmentation in a total of 266 participants. The duration of patient follow-up after treatment was 2.7 ± 2.4 years. The meta-analysis demonstrated a clinically significant risk difference of 0.67 (95% CI: 0.61–0.73) with an absolute risk of 670 events/1,000 patients (95% CI: 610–730 events/1,000 patients) with use of ropinirole (see **Figure S102**).

A meta-analysis of 4 RCTs[110,112,113,115] reported on the incidence of somnolence in a total of 1,430 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a clinically significant risk difference of 0.06 (95% CI: 0.01–0.11) with an absolute risk of 60 events/1,000 patients (95% CI: 10–110 events/1,000) with use of ropinirole (see **Figure S103**).

A meta-analysis of 4 RCTs[108,110,112,116] reported on the incidence of dizziness in a total of 1,315 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a clinically significant risk difference of 0.07 (95% CI: 0.04–0.09) with an absolute risk of 70 events/1,000 patients (95% CI: 40–90 events/1,000) with use of ropinirole (see **Figure S104**).

The certainty of evidence for unwanted side effects ranged from low to moderate due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of ropinirole in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S14**).

Benefits vs harms

The potential benefits of ropinirole in adults with RLS include clinically significant improvements in disease severity and QoL. The potential harms include a clinically significant risk of somnolence, dizziness and augmentation that may or may not resolve over time. The TF judged that the potential harms of ropinirole in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for ropinirole ranges from $0.04 for a 0.25 mg tablet to $0.14 for a 5 mg tablet.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant risks, the TF judged that most adults with RLS would generally not be accepting of treatment with ropinirole.

Bupropion

One RCT[119] investigated the use of bupropion in adults with RLS to improve 1 or more of the following outcomes: disease severity and unwanted side effects. Participants in the RCT (29:31 intervention: control group) received 150 mg of sustained-release bupropion for 6 weeks. Participants had a mean age of 49 years (77% female). Meta-analyses were performed to assess the efficacy of bupropion as a treatment for adults with RLS. The meta-analyses are provided in **Figure S105** and **Figure S106**. A summary of findings table is provided in **Table S15**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of bupropion to treat adults with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of bupropion to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 1 RCT[119] in a total of 60 participants. The duration of patient follow-up after treatment was 3 weeks. The meta-analysis demonstrated a nonclinically significant reduction in disease severity of −2.8 points (95% CI: −7.3 to 1.7 points) as measured by the IRLS (see **Figure S105**). The certainty of evidence was moderate due to imprecision.

Adverse effects: A meta-analysis of 1 RCT[119] reported on the total adverse events that led to study withdrawal in a total of 60 participants. The duration of patient follow-up after treatment ranged was 3–6 weeks. The meta-analysis demonstrated a nonclinically significant risk ratio of 1.1 (95% CI: 0.3–3.9) with an absolute risk of 13 events/1,000 patients (95% CI: −92 to 374 events/1,000 patients) with use of bupropion (see **Figure S106**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of bupropion in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S15**).

Benefits vs harms

The potential benefits of bupropion in adults with RLS were considered trivial. Side effects including nausea and gastritis have been reported. The TF judged that the balance of potential benefits and harms in adults with RLS does not favor either bupropion or the comparison.

Resource use

The current unit costs for bupropion ranges from $0.07 for a 150 mg tablet to $8.89 for a 450 mg tablet.[34] The TF judged these costs to be negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given there was no clinically significant improvement in disease severity, the TF judged that most adults with RLS would generally not be accepting of treatment with bupropion.

Carbamazepine

A total of 2 RCTs[120,121] and 1 observational study[122] investigated the use of carbamazepine in adults with RLS to improve 1 or more of the following outcomes: disease severity, PLM frequency, sleep latency, WASO, and unwanted side effects. Participants in the RCTs received 100–300 mg of carbamazepine. Participants had a mean age of 53 years (69% female). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving 3–7 mg/kg of carbamazepine per day. Meta-analyses were performed to assess the efficacy of carbamazepine as a treatment for adults with RLS. The meta-analyses are provided in **Figure S107** through **Figure S114**. A summary of findings table is provided in **Table S16**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of carbamazepine to treat adults with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of carbamazepine to reduce disease severity as measured by RL sensation frequency was

reported in 1 RCT[120] in a total of 12 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a reduction in disease severity of −1.1 day/wk (95% CI: −3.1 to 0.9) (see **Figure S107**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

The efficacy of carbamazepine to reduce disease severity as measured by self-reported severity ratings was reported in 1 RCT[120] in a total of 12 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a reduction in disease severity of −3.0 (95% CI: −8.7 to 2.7) (see **Figure S108**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a CST for this measure. The certainty of evidence was moderate due to imprecision.

Adverse effects: A meta-analysis of 2 RCTs[120,121] reported on the total adverse events that led to study withdrawal in a total of 184 participants. The duration of patient follow-up after treatment ranged from 4–5 weeks. The meta-analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.05 (95% CI: −0.02 to 0.11) with an absolute risk of 50 events/1,000 patients (95% CI: −20 to 110 events/1,000 patients) with use of carbamazepine (see **Figure S109**).

One observational study[122] reported on the total adverse events that led to study withdrawal in a total of 9 participants. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: −0.19 to 0.19) with an absolute risk of 0 events/1,000 patients (95% CI: −190 to 190 events/1,000 patients) with use of carbamazepine (see **Figure S110**).

One RCT[120] reported on the incidence of dizziness in a total of 12 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.17 (95% CI: −0.19 to 0.53) with an absolute risk of 170 events/1,000 patients (95% CI: 190–530 events/1,000 patients) with use of carbamazepine (see **Figure S111**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of carbamazepine: sleep latency, WASO, and PLM frequency.

PLM frequency: The efficacy of carbamazepine to decrease PLM frequency was reported in 1 observational study[122] in a total of 9 participants. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated an increase of 1.4 PLMs/h (95% CI: −19.3 to 22.1 PLMs/h) as measured by the myoclonus index (see **Figure S112**). The clinical significance of this increase was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Sleep latency: The efficacy of carbamazepine to decrease sleep latency was reported in 1 observational study[53] in a total of 9 participants. The duration of patient follow-up after treatment was 6 weeks. Meta-analysis demonstrated a clinically significant decrease of −25.7 minutes (95% CI: −48.3 to 3.1 minutes) (see **Figure S113**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

WASO: The efficacy of carbamazepine to decrease WASO was reported in 1 observational study[122] in a total of 9 participants. The duration of patient follow-up after treatment was 6 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of −65.1 minutes (95% CI: −126.4 to −3.8 minutes) with carbamazepine (see **Figure S114**). The certainty of evidence very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of carbamazepine in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S16**).

Benefits vs harms

The potential benefits of carbamazepine in adults with RLS include a reduction in disease severity (not measured by IRLS or validated measure), sleep latency, and WASO. The potential harms include a clinically significant risk of dizziness that may or may not resolve over time. The TF acknowledged additional risks not limited to hepatotoxicity and adverse hematopoietic effects. The TF judged that the potential harms of carbamazepine in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for carbamazepine ranges from $0.31 for a 100 mg tablet to $5.19 for a 400 mg tablet.[34] The TF judged these costs as moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. The TF judged that most adults with RLS would generally not be accepting of treatment with carbamazepine.

Clonazepam

A total of 3 RCTs[54–56] investigated the use of clonazepam in adults with RLS to improve 1 or more of the following outcomes: sleep latency, PLM frequency, WASO, and unwanted side effects. Participants in the RCTs received 0.5–2 mg of clonazepam. Participants had a mean age of 52 years (53% female). Meta-analyses were performed to assess the efficacy of clonazepam as a treatment for adults with RLS. The meta-analyses are provided in **Figure S115** through **Figure S119**.

A summary of findings table is provided in **Table S17**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of clonazepam to treat adults with RLS: unwanted side effects.

Adverse effects: A meta-analysis of 3 RCTs[123–125] reported on the total adverse events that led to study withdrawal in a total of 44 participants. The duration of patient follow-up after treatment ranged from 3 days to 4 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI −0.13 to 0.13) with an absolute risk of 0 events/1,000 patients (95% CI: −130 to 130 events/1,000 patients) with use of clonazepam (see **Figure S115**).

One RCT[125] reported on the incidence of sleepiness in a total of 12 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.33 (95% CI: −0.17 to 0.83) with an absolute risk of 330 events/1,000 patients (95% CI: −170 to 830 events/1,000 patients) with use of clonazepam (see **Figure S116**).

The certainty of evidence for unwanted side effects was moderate.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of clonazepam: PLM frequency, sleep latency, and WASO.

PLM frequency: The efficacy of clonazepam to decrease PLM frequency was reported in 1 RCT[125] in a total of 20 participants. The duration of patient follow-up after treatment was 3 days. The meta-analysis demonstrated a decrease of −0.6 PLMs/h (95% CI: −20.7 to 19.4 PLMs/h) as measured by the PLMI (see **Figure S117**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate.

Sleep latency: The efficacy of clonazepam to decrease sleep latency was reported in 1 RCT[125] in a total of 20 participants. The duration of patient follow-up after treatment was 3 days. Meta-analysis demonstrated a nonclinically significant decrease of −3.2 minutes (95% CI: −14.8 to 8.4 minutes) (see **Figure S118**). The certainty of evidence was moderate.

WASO: The efficacy of clonazepam to decrease WASO was reported in 1 RCT[125] in a total of 20 participants. The duration of patient follow-up after treatment ranged from 2–12 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of −68.6 minutes (95% CI: −114.6 to −22.6 minutes) with clonazepam (see **Figure S119**). The certainty of evidence was moderate.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of clonazepam in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S17**).

Benefits vs harms

The potential benefits of clonazepam in adults with RLS could not be determined due to lack of evidence in critical outcomes with validated metrics. The potential harms include the risk of sleepiness that may or may not resolve over time. The TF acknowledged risks of cognitive impairment and chemical dependence. No risk of augmentation was reported. The TF judged that the potential harms of clonazepam in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for clonazepam ranges from $0.02 for a 0.5 mg tablet to $1.17 for a 2 mg tablet.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is important uncertainty or variability in how much patients value the main outcomes. The TF judged that most adults with RLS would generally not be accepting of treatment with clonazepam.

Valerian

One RCT[126] investigated the use of valerian in adults with RLS to improve 1 or more of the following outcomes: disease severity, sleep quality, and unwanted side effects. Participants in the RCT received 800 mg of valerian. Participants had a mean age of 49 years (75% female). Meta-analyses were performed to assess the efficacy of valerian as a treatment for adults with RLS. The meta-analyses are provided in **Figure S120** through **Figure S123**. A summary of findings table is provided in **Table S18**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of valerian to treat adults with RLS: disease severity, sleep quality, and unwanted side effects.

Disease severity: The efficacy of valerian to reduce disease severity as measured by IRLS was reported in 1 RCT[126] in a total of 37 participants. The duration of patient follow-up after treatment was 8 weeks. The meta-analysis demonstrated a nonclinically significant increase in disease severity of 1.3 points (95% CI: −5.1 to 7.7 points) as measured by the IRLS (see **Figure S120**). The certainty of evidence was low due to very serious imprecision.

Sleep quality: The efficacy of valerian to improve sleep quality was evaluated based on 1 RCT[126] that reported on the PSQI scale in a total of 37 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a nonclinically significant decline in sleep quality of 0.1 points (95% CI: −3.2 to 3.4) as measured by the PSQI scale (see **Figure S121**). The certainty of evidence was low due to very serious imprecision.

Adverse effects: One RCT[126] reported on the total adverse events that led to study withdrawal in a total of 37 participants.

The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.08 (95% CI: −0.07 to 0.24) with an absolute risk of 80 events/1,000 patients (95% CI: −70 to 240 events/1,000 patients) with use of valerian (see **Figure S122**).

One RCT[126] reported on the incidence of dizziness in a total of 24 participants. The duration of patient follow-up after treatment was 8 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.04 (95% CI: −0.07 to 0.15) with an absolute risk of 40 events/1,000 patients (95% CI: −70 to 150 events/1,000 patients) with use of valerian (see **Figure S123**).

The certainty of evidence for unwanted side effects was low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of valerian in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S18**).

Benefits vs harms

The potential benefits of valerian in adults with RLS were considered trivial by the TF. The potential harms include a clinically significant risk of dizziness that may or may not resolve over time. No risk of augmentation was reported. The TF judged that the potential harms of valerian in adults with RLS outweigh the potential benefits.

Resource use

The TF judged the costs of valerian are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the trivial benefits and potential harms, the TF judged that most adults with RLS would generally not be accepting of treatment with valerian.

Valproic acid

One observational study[64] investigated the use of valproic acid in adults with RLS to improve 1 or more of the following outcomes: disease severity, PLM frequency, WASO, and unwanted side effects. The observational study was a before-and-after treatment design with participants diagnosed with moderate to severe RLS, receiving 600 mg valproic acid, and serving as their own controls. Analyses were performed to assess the efficacy of valproic acid as a treatment for adults with RLS. The analyses are provided in **Figure S124** through **Figure S128**. A summary of findings table is provided in **Table S19**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of valproic acid to treat adults with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of valproic acid to reduce disease severity as measured by RLS intensity score was reported in 1 observational study[64] in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The results demonstrated a reduction in disease severity of −1.7 (95% CI: −3.9 to 0.5) (see **Figure S124**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

The efficacy of valproic acid to reduce disease severity as measured by RLS duration was reported in 1 observational study[64] in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The results demonstrated a reduction in disease severity of −51.5 minutes (95% CI: −292.8 to 189.8) (see **Figure S125**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

The certainty of evidence for disease severity was low due to imprecision.

Adverse effects: One observational study[64] reported on the total adverse events that led to study withdrawal in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: −0.24 to 0.24) with an absolute risk of 0 events/1,000 patients (95% CI: −240 to 240 events/1,000 patients) with use of valproic acid (see **Figure S126**). The certainty of evidence was low due to very serious imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of valproic acid: WASO and PLM frequency.

PLM frequency: The efficacy of valproic acid to decrease PLM frequency was reported in 1 observational study[64] in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The results demonstrated a decrease of −5.2 PLMs/h (95% CI: −41.5 to 31.1 PLMs/h) as measured by the PLMI (see **Figure S127**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was low due to very serious imprecision.

WASO: The efficacy of valproic acid to decrease WASO was reported in 1 observational study[64] in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The results demonstrated a nonclinically significant decrease in WASO of −3.3 minutes (95% CI: −22.4 to 15.8 minutes) with valproic acid (see **Figure S128**). The certainty of evidence was low due to very serious imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of valproic acid in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S19**).

Benefits vs harms

The potential benefits of valproic acid in adults with RLS include changes in disease severity and WASO. There were changes in PLM frequency of uncertain clinical significance as no CST was set. No risk of augmentation was reported. The TF acknowledged additional risks not limited to hepatotoxicity and teratogenicity. The TF judged that the potential harms of valproic acid in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for valproic acid ranges from $0.03 for a 250 mg/5 mL solution to $0.26 for a 250 mg capsule.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is important uncertainty or variability in how much patients value the main outcomes. Given the potential harms, the TF judged that most adults with RLS would generally not be accepting of treatment with valproic acid.

Cabergoline

A total of 2 RCTs[127,128] and 4 observational studies[71,128–130] investigated the use of cabergoline in adults with RLS to improve 1 or more of the following outcomes: disease severity, QOL, PLM frequency, sleep latency, and unwanted side effects. Participants in the RCTs had a mean age of 56 years (71% female) and were diagnosed with moderate to severe RLS. Participants received titrated dosages of cabergoline from 0.25–2 mg. All observational studies were before-and-after treatment design with participants diagnosed with moderate to severe RLS and serving as their own controls. Meta-analyses were performed to assess the efficacy of cabergoline as a treatment for adults with RLS. The meta-analyses are provided in **Figure S129** through **Figure S135**. A summary of findings table is provided in **Table S20**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of cabergoline to treat adults with RLS: disease severity, QOL, and unwanted side effects.

Disease severity: The efficacy of cabergoline to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 RCTs[127,128] in a total of 124 participants. The duration of patient follow-up after treatment ranged from 5–47 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −12.5 points (95% CI: −17.2 to −7.9 points) as measured by the IRLS (see **Figure S129**). The certainty of evidence was moderate due to imprecision.

QOL: The efficacy of cabergoline to improve QOL was reported in 1 RCT[127] on the RLS-QOL Kohnen scale in a total of 40 participants. The duration of patient follow-up after treatment was 5 weeks. The analysis demonstrated a clinically significant improvement in QOL of −12.3 points (95% CI: −22.3 to 2.3 points) as measured by the RLS-QOL Kohnen scale (see **Figure S130**). The certainty of evidence was moderate due to imprecision.

Adverse effects: A meta-analysis of 2 RCTs[127,128] reported on the total adverse events that led to study withdrawal in a total of 128 participants. The duration of patient follow-up after treatment ranged from 5–47 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 4.4 (95% CI: 0.6–34.4) with an absolute risk of 0 events/1,000 patients (95% CI: 0–0 events/1,000 patients) with use of cabergoline (see **Figure S131**).

A meta-analysis of 4 observational studies[71,128–130] reported on the incidence of augmentation in a total of 558 participants. The duration of patient follow-up after treatment ranged from 5–30 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 12.1 (95% CI: 2.2–65.7) with an absolute risk of 36 events/1,000 patients (95% CI: 21–51events/1,000 patients) with use of cabergoline (see **Figure S132**).

A meta-analysis of 2 RCTs[127,128] reported on the incidence of dizziness or vertigo in a total of 128 participants. The duration of patient follow-up after treatment ranged from 5–47 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 0.73 (95% CI: 0.02–25.58) with an absolute risk of 26 events/1,000 patients (95% CI: −93 to 1,000 events/1,000 patients) with use of cabergoline (see **Figure S133**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies, imprecision, and inconsistency.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of cabergoline: PLM frequency and sleep latency.

PLM frequency: The efficacy of cabergoline to decrease PLM frequency was evaluated reported in 1 RCT[127] in a total of 40 participants. The duration of patient follow-up after treatment was 5 weeks. The meta-analysis demonstrated a decrease of −32.8 PLMs/h (95% CI: −56.8 to −8.8 PLMs/h) as measured by the PLMI (see **Figure S134**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

Sleep latency: The efficacy of cabergoline to decrease sleep latency was evaluated reported in 1 RCT[127] in a total of 40 participants. The duration of patient follow-up after treatment was 5 weeks. Meta-analysis demonstrated a clinically significant increase of 17.7 minutes (95% CI: −6.9 to 42.3 minutes) favoring placebo (see **Figure S135**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of cabergoline in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies, imprecision, and inconsistency (see **Table S20**).

Benefits vs harms

The potential benefits of cabergoline in adults with RLS include a clinically significant improvement in disease severity, QOL and sleep latency. The potential harms include a clinically significant risk of dizziness/vertigo and augmentation that may or may not resolve over time. Other side effects including nausea, depression, and valvular heart disease have been reported.[131,132] The TF acknowledged the substantial clinical risk of valvular heart disease. The TF judged that the potential harms of cabergoline in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for cabergoline ranges from $2.44–$2.87 for a 0.5 mg tablet.[34] The TF judged these costs are moderate.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. The TF judged that adults with RLS would not be accepting of treatment with cabergoline.

PICO 2: ADULT POPULATIONS WITH RLS AND ESRD

Gabapentin

One RCT[133] and 2 observational studies[134,135] investigated the use of gabapentin in adults with RLS and ESRD to improve 1 or more of the following outcomes: disease severity, sleep quality, and unwanted side effects. Participants in the RCT received dosages of gabapentin 300 mg 3 times weekly after hemodialysis. Participants had a mean age of 64 years (94% male). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving dosages of 200 mg gabapentin 3 times weekly after hemodialysis. Meta-analyses were performed to assess the efficacy of gabapentin as a treatment for adults with RLS and ESRD. The meta-analyses are provided in **Figure S136** through **Figure S141**. A summary of findings table is provided in **Table S21**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of gabapentin to treat adults with RLS and ESRD: disease severity, sleep quality, and unwanted side effects.

Disease severity: The efficacy of gabapentin to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 observational studies[134,135] in a total of 56 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −18.6 points (95% CI: −21.6 to −15.5 points) as measured by the IRLS (see **Figure S136**). The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

Sleep quality: The efficacy of gabapentin to improve sleep quality was evaluated based on an analysis of 2 observational studies[134,135] that reported on the PSQI scale in a total of 56 participants. The duration of patient follow-up after treatment was 4 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of −10.3 points (95% CI: −13.3 to −7.3) as measured by the PSQI scale (see **Figure S137**. The certainty of evidence for sleep quality was very low due to risk of bias associated with observational studies and imprecision.

Adverse effects: One RCT[133] reported on the total adverse events that led to study withdrawal in a total of 16 participants. The duration of patient follow-up after treatment was 6 weeks. The results demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.13 (95% CI: −0.06 to 0.31) with an absolute risk of 130 events/1,000 patients (95% CI: −60 to 310 events/1,000 patients) with use of gabapentin (see **Figure S138**).

A meta-analysis of 2 observational studies[134,135] reported on the total adverse events that led to study withdrawal in a total of 58 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of 0.03 (95% CI: −0.03 to 0.10) with an absolute risk of 30 events/1,000 patients (95% CI: −30 to 100 events/1,000) with use of gabapentin (see **Figure S139**).

One RCT[133] reported on the incidence of somnolence in a total of 16 participants. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.13 (95% CI: −0.06 to 0.31) with an absolute risk of 130 events/1,000 patients (95% CI: −60 to 310 events/1,000 patients) with use of gabapentin (see **Figure S140**).

One observational study[135] reported on the incidence of somnolence in a total of 44 participants. The duration of patient follow-up after treatment was 4 weeks. The analysis demonstrated a clinically significant risk difference of 0.14 (95% CI: 0.03–0.24) with an absolute risk of 140 events/1,000 patients (95% CI: 30–240 events/1,000) with use of gabapentin (see **Figure S141**).

The certainty of evidence for adverse effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of gabapentin in adults with RLS and ESRD was very low based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S21**).

Benefits vs harms

The potential benefits of gabapentin in adults with RLS and ESRD include a clinically significant improvement in disease severity and sleep quality. The potential harms include a clinically significant risk of somnolence that may or may not resolve over time. No risk of augmentation was reported. The TF judged that the potential benefits of gabapentin in adults with RLS and ESRD outweigh the potential harms.

Resource use

The current unit costs for gabapentin ranges from $0.03 for a 100 mg capsule to $0.13 for a 800 mg tablet.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS and ESRD would generally be accepting of treatment with gabapentin.

IV Iron sucrose

One RCT[136] investigated the use of IV iron sucrose in adults with RLS and ESRD to improve 1 or more of the following outcomes: disease severity. Participants in the RCT received 1,000 mg of iron sucrose. Participants had a mean age of 63 years with 20 females and 12 males. Analyses were performed to assess the efficacy of IV iron sucrose as a treatment for adults with RLS and ESRD. The analyses are provided in **Figure S142** and **Figure S143**. A summary of findings table is provided in **Table S22**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV iron sucrose to treat adults with RLS: disease severity and adverse effects.

Disease severity: The efficacy of IV iron sucrose to reduce disease severity as measured by the IRLS was reported in 1 RCT[136] in a total of 32 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated a clinically significant reduction in disease severity of −6.6 points (95% CI: −8.2 to −5.0 points) as measured by the IRLS (see **Figure S142**). The certainty of evidence was moderate due to small sample size.

Adverse effects: One RCT[136] reported on the total adverse events that led to study withdrawal in a total of 32 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.0 (95% CI: −0.11 to 0.11) with an absolute risk of 0 events/1,000 patients (95% CI: −110 to 110 events/1,000 patients) with use of IV iron sucrose (see **Figure S143**).

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV iron sucrose in adults with RLS and ESRD was moderate based on the critical outcomes and downgrading of the evidence due to small sample size (see **Table S22**).

Benefits vs harms

The potential benefits of IV iron sucrose in adults with RLS and ESRD include a clinically significant improvement in disease severity. The TF judged that the potential benefits of IV iron sucrose in adults with RLS and ESRD outweigh the potential harms.

Resource use

The TF judged the costs for IV iron sucrose to be moderate due to cost of infusion at a treatment center.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS and ESRD would generally be accepting of treatment with IV iron sucrose.

Vitamin C

One RCT[137] investigated the use of vitamin C in adults with RLS and ESRD to improve 1 or more of the following outcomes: disease severity. Participants in the RCT received 200 mg of vitamin C. Participants had a mean age of 56 years (1:1 female-to-male). Meta-analyses were performed to assess the efficacy of vitamin C as a treatment for adults with RLS and ESRD. The meta-analyses are provided in **Figure S144**. A summary of findings table is provided in **Table S23**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of vitamin C to treat adults with RLS: disease severity.

Disease severity: The efficacy of vitamin C to reduce disease severity as measured by the IRLS was reported in 1 RCT[137] in a total of 30 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant reduction in disease severity of −6.9 points (95% CI: −9.2 to −4.6 points) as measured by the IRLS (see **Figure S144**). The certainty of evidence was low due to imprecision and indirectness.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of vitamin C in adults with RLS and ESRD was low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness (see **Table S23**).

Benefits vs harms

The potential benefits of vitamin C in adults with RLS and ESRD include a clinically significant improvement in disease severity. No risk of augmentation was reported. The TF judged that the potential benefits of vitamin C in adults with RLS and ESRD outweigh the potential harms.

Resource use

The TF judged the costs for vitamin C are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes.

Given the clinically significant improvement in disease severity, the TF judged that most adults with RLS and ESRD would generally be accepting of treatment with vitamin C.

Levodopa

One RCT[65] and 4 observational studies[134,135,138,139] investigated the use of levodopa in adults with RLS and ESRD to improve 1 or more of the following outcomes: disease severity, sleep quality, PLM frequency, and unwanted side effects. Participants in the RCT received 100 mg or 200 mg/50 mg of levodopa (with phosphodiesterase inhibitor carbidopa or benserazide). Participants had a mean age of 52 years (56% male). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving 100–200 mg of levodopa (with phosphodiesterase inhibitor carbidopa or benserazide). Meta-analyses were performed to assess the efficacy of levodopa as a treatment for adults with RLS and ESRD. The meta-analyses are provided in **Figure S145** through **Figure S150**. A summary of findings table is provided in **Table S24**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of levodopa to treat adults with RLS and ESRD: disease severity, sleep quality, and unwanted side effects.

Disease severity: The efficacy of levodopa to reduce disease severity as measured by the CGI-S was reported in 1 RCT[65] in a total of 11 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a nonclinically significant improvement of −0.2 (95% CI: −1.0 to 0.6) as measured by the CGI-S (see **Figure S145**).

The efficacy of levodopa to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 observational studies[134,135] in a total of 52 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −14.1 points (95% CI: −16.4 to −11.9 points) as measured by the IRLS (see **Figure S146**).

The certainty of evidence for disease severity ranged from very low to low due to risk of bias associated with observational studies and imprecision.

Sleep quality: The efficacy of levodopa to improve sleep quality was evaluated based on an analysis of 2 observational studies[134,135] that reported on the PSQI scale in a total of 52 participants. The duration of patient follow-up after treatment was 4 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of −7.2 points (95% CI: −10.1 to −4.3) as measured by the PSQI scale (see **Figure S147**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Adverse effects: There were no adverse events leading to study withdrawal reported from the 11 participants in the 1 RCT.[65] The duration of patient follow-up after treatment ranged was 4 weeks (see **Figure S148**).

A meta-analysis of 3 observational studies[134,135,138,139] reported on the total adverse events that led to study withdrawal in a total of 69 participants. The duration of patient follow-up after treatment ranged from 4–14 weeks. The meta-analysis demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.02 (95% CI: −0.03 to 0.08) with an absolute risk of 20 events/1,000 patients (95% CI: −30 to 80 events/1,000 patients) with use of levodopa (see **Figure S149**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of levodopa: PLM frequency.

PLM frequency: The efficacy of levodopa to decrease PLM frequency was reported in 1 RCT[65] in a total of 11 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a decrease of −28.0 PLMs/h (95% CI: −75.0 to 18.9 PLMs/h) as measured by the PLMI (see **Figure S150**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of levodopa in adults with RLS and ESRD was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S24**).

Benefits vs harms

The potential benefits of levodopa in adults with RLS and ESRD include a clinically significant improvement in disease severity and sleep quality, and improvement in PLM frequency. The results also reported significant results of adverse events leading to study withdrawal. The TF acknowledged the substantial risk of augmentation. The TF judged that the potential harms of levodopa in adults with RLS and ESRD outweigh the potential benefits.

Resource use

The current unit costs for levodopa was $0.07 for a 25/100 mg tablet.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the potential harms with augmentation, the TF judged that most adults with RLS and ESRD would generally not be accepting of treatment with levodopa.

Rotigotine

One RCT[140] investigated the use of rotigotine in adults with RLS and ESRD to improve 1 or more of the following outcomes: disease severity, QOL, PLM frequency, sleep latency, WASO, and unwanted side effects. Participants in the RCT had a mean age of 55 years (67% male) and were diagnosed with moderate to severe RLS. Participants received dosages of transdermal rotigotine from 1–3 mg. Meta-analyses were performed to assess the efficacy of rotigotine as a treatment for adults with RLS and ESRD. The meta-analyses are provided in **Figure S151** through **Figure S156**. A summary of findings table is provided in **Table S25**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of rotigotine to treat adults with RLS and ESRD: disease severity, QOL, and unwanted side effects.

Disease severity: The efficacy of rotigotine to reduce disease severity as measured by the IRLS was reported in 1 RCT[140] in a total of 25 participants. The duration of patient follow-up after treatment was 5 weeks. The results demonstrated a clinically significant reduction in disease severity of −7.3 points (95% CI: −13.7 to −0.9 points) as measured by the IRLS (see **Figure S151**). The certainty of evidence was moderate due to imprecision.

QOL: The efficacy of rotigotine to improve QOL was evaluated in 1 RCT[140] that reported on the RLS-QOL Kohnen scale in a total of 25 participants. The duration of patient follow-up after treatment was 5 weeks. The analysis demonstrated a non-clinically significant improvement in QOL of 0.5 points (95% CI: −8.2 to 9.2 points) as measured by the RLS-QOL Kohnen scale (see **Figure S152**). The certainty of evidence was moderate due to imprecision.

Adverse effects: One RCT[140] reported on the total adverse events that led to study withdrawal in a total of 30 participants. The duration of patient follow-up after treatment was 5 weeks. The results demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.10 (95% CI: −0.09 to 0.29) with an absolute risk of 100 events/1,000 patients (95% CI: −90 to 290 events/1,000 patients) with use of rotigotine (see **Figure S153**). The certainty of evidence was low due to very serious imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of rotigotine: PLM frequency, sleep latency, and WASO.

PLM frequency: The efficacy of rotigotine to decrease PLM frequency was evaluated using a meta-analysis of 1 RCT[140] in a total of 25 participants. The duration of patient follow-up after treatment ranged was 5 weeks. The results demonstrated a decrease of −34.0 PLMs/h (95% CI: −57.5 to −10.5 PLMs/h) as measured by the PLMI (see **Figure S154**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

Sleep latency: The efficacy of rotigotine to decrease sleep latency was reported in 1 RCT[140] in a total of 25 participants. The duration of patient follow-up after treatment was 5 weeks. The results demonstrated a clinically significant decrease of −31.7 minutes (95% CI: −79.2 to 15.8 minutes) (see **Figure S155**). The certainty of evidence was low due to very serious imprecision.

WASO: The efficacy of rotigotine to decrease WASO was reported in 1 RCT[140] in a total of 25 participants. The duration of patient follow-up after treatment was 5 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of −22.8 minutes (95% CI: −64.2 to −18.6 minutes) with rotigotine (see **Figure S156**). The certainty of evidence was low due to very serious imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of rotigotine in adults with RLS and ESRD was very low based on the critical outcomes and downgrading of the evidence due to serious imprecision (see **Table S25**).

Benefits vs harms

The potential benefits of rotigotine in adults with RLS and ESRD include a clinically significant reduction in disease severity, QOL, sleep latency, and WASO, and improvement in PLM frequency. Side effects including nausea, headache, and asthenia have been reported with the rotigotine transdermal patch.[105] Augmentation was not considered; however, the study duration was insufficient (5 weeks) to properly assess augmentation. The TF acknowledged the risk of augmentation with long-term use. The TF judged that the potential harms outweigh the potential benefits in adults with RLS and ESRD.

Resource use

The current unit costs of rotigotine ranges from $22.66 for a 4 mg/24 hours patch to $22.88 for a 8 mg/24 hours patch.[34] The TF judged these costs are moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. The TF judged that most adults with RLS and ESRD would generally not be accepting of treatment with rotigotine.

PICO 3: ADULTS WITH PLMD

Triazolam

A total of 2 RCTs[141,142] investigated the use of triazolam in adults with PLMD to improve 1 or more of the following outcomes: excessive daytime sleepiness, sleep latency, WASO, PLM frequency, and unwanted side effects. Participants in the RCTs had a mean age of 53 years (67% male). Participants received 0.25–0.5 mg triazolam. Meta-analyses were performed to assess the efficacy of triazolam as a treatment for adults with PLMD.

The meta-analyses are provided in **Figure S157** through **Figure S161**. A summary of findings table is provided in **Table S26**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of triazolam to treat adults with PLMD: excessive daytime sleepiness and unwanted side effects.

Excessive daytime sleepiness: The efficacy of triazolam to improve excessive daytime sleepiness was evaluated from an analysis of 1 RCT[142] that reported on the multiple sleep latency test in a total of 24 participants. The duration of patient follow-up after treatment ranged from 4–7 days. The analysis demonstrated a clinically significant improvement in excessive daytime sleepiness of 3.4 minutes (95% CI: −0.1 to 6.9) as measured by the multiple sleep latency test (see **Figure S157**). The certainty of evidence was moderate due to imprecision.

Adverse effects: A meta-analysis of 2 RCTs[142] reported on the total adverse events that led to study withdrawal in a total of 24 participants. The duration of patient follow-up after treatment ranged from 4 days to 12 weeks. In both studies there were no adverse events leading to study withdrawal with use of triazolam (see **Figure S158**). The certainty of evidence was moderate due to imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of triazolam: PLM frequency, sleep latency, and WASO.

PLM frequency: The efficacy of triazolam to decrease PLM frequency was reported in 1 RCT[142] in a total of 15 participants. The duration of patient follow-up after treatment ranged from 4–7 days. The meta-analysis demonstrated a decrease of −21.3 PLMs/h (95% CI: −44.5 to 1.9 PLMs/h) as measured by the PLMI (see **Figure S159**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

Sleep latency: The efficacy of triazolam to decrease sleep latency was reported in 1 RCT[142] in a total of 15 participants. The duration of patient follow-up after treatment ranged from 4–7 days. The results demonstrated a nonclinically significant increase of 1.7 minutes (95% CI: −1.06 to 4.5 minutes) (see **Figure S160**). The certainty of evidence was moderate due to imprecision.

WASO: The efficacy of triazolam to decrease WASO was reported in 1 RCT[142] in a total of 15 participants. The duration of patient follow-up after treatment ranged from 4–7 days. Results demonstrated a clinically significant increase in WASO of 11.7 minutes (95% CI: −8.5 to 31.9 minutes) with triazolam (see **Figure S161**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of triazolam in adults with PLMD was very low based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S26**).

Benefits vs harms

The potential benefits of triazolam in adults with PLMD include a clinically significant improvement in excessive daytime sleepiness. The TF judged that the balance of potential benefits and harms in adults with PLMD does not favor either triazolam or the comparison.

Resource use

The current unit costs for triazolam ranges from $0.33 for a 0.125 mg tablet to $0.74 for a 0.25 mg tablet.[34] The TF judged the costs of triazolam are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence for benefits, the TF judged that most adults with PLMD would generally not be accepting of treatment with triazolam.

Valproic acid

One observational study[143] investigated the use of valproic acid in adults with PLMD to improve 1 or more of the following outcomes: PLM frequency and unwanted side effects. The observational study is a before-and-after treatment design with participants receiving 150–600 mg of valproic acid and serving as their own controls. Analyses were performed to assess the efficacy of valproic acid as a treatment for adults with PLMD. The results are provided in **Figure S162** and **Figure S163**. A summary of findings table is provided in **Table S27**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of valproic acid to treat adults with PLMD: unwanted side effects.

Adverse effects: One observational study[143] reported on the total adverse events that led to study withdrawal in a total of 6 participants. The duration of patient follow-up after treatment ranged from 3 months to 3 years. The results demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.33 (95% CI: −0.07 to 0.74) with an absolute risk of 330 events/1,000 patients (95% CI: −70 to 740 events/1,000 patients) with use of valproic acid (see **Figure S162**). The certainty of evidence was very low due to imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of valproic acid: PLM frequency.

PLM frequency: The efficacy of valproic acid to decrease PLM frequency was reported in 1 observational study[143] in a total of 6 participants. The duration of patient follow-up after

treatment ranged from 3 months to 3 years. The meta-analysis demonstrated a decrease of −11.3 PLMs/h (95% CI: −17.5 to −5.1 PLMs/h) as measured by the PLMI (see **Figure S163**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was very low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of valproic acid in adults with PLMD was very low based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S27**).

Benefits vs harms

The potential benefits of valproic acid in adults with PLMD include an improvement in PLM frequency. The TF acknowledged additional risks not limited to hepatotoxicity and teratogenicity. The TF judged that the potential harms of valproic acid in adults with PLMD outweigh the potential benefits.

Resource use

The current unit costs for valproic acid ranges from $0.03 for a 250 mg/5 ml solution to $0.26 for a 250 mg capsule.[34] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. The TF judged that most adults with PLMD would generally not be accepting of treatment with valproic acid.

PICO 4: PEDIATRIC POPULATIONS WITH RLS

Ferrous sulfate

A total of 2 observational studies[144,145] investigated the use of ferrous sulfate in children with RLS to improve 1 or more of the following outcomes: disease severity and unwanted side effects. One observational study is a retrospective design and 1 is a clinical cohort. All participants received 3mg/kg/d of ferrous sulfate and served as their own controls. Meta-analyses were performed to assess the efficacy of oral iron as a treatment for children with RLS. The meta-analyses are provided in **Figure S164** through **Figure S168**. A summary of findings table is provided in **Table S28**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of ferrous sulfate to treat children with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of ferrous sulfate to reduce disease severity as measured by the P-RLS-SS was reported in 1 observational study[145] in a total of 16 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a reduction in disease severity of −2.5 points (95% CI: −4.7 to −0.3 points) as measured by the P-RLS-SS (see **Figure S164**). The clinical significance of this reduction was not determined as the TF could not reasonably estimate a threshold for this measure.

The efficacy of ferrous sulfate to reduce disease severity as measured by the IRLS reported 1 observational study[144] in a total of 21 participants. The duration of patient follow-up after treatment ranged from 1–2 years. The results demonstrated a clinically significant reduction in disease severity of −10.5 points (95% CI: −15.4 to −5.6 points) as measured by the IRLS (see **Figure S165**).

The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

Adverse effects: One observational study[145] reported on the total adverse events that led to study withdrawal in a total of 65 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a nonclinically significant risk difference of adverse events leading to study withdrawal of 0.02 (95% CI: −0.03 to 0.06) with an absolute risk of 20 events/1,000 patients (95% CI: −30 to 60 events/1,000 patients) with use of ferrous sulfate (see **Figure S166**).

One observational study[144] reported on the total adverse events that led to study withdrawal in a total of 30 participants. The duration of patient follow-up after treatment ranged from 1–2 years. The results reported of no adverse events leading to study withdrawal with use of ferrous sulfate (see **Figure S167**).

The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of ferrous sulfate to treat children with RLS: PLM frequency.

PLM frequency: The efficacy of oral iron to decrease PLM frequency was evaluated using a meta-analysis of 1 observational study[144] in a total of 21 participants. The duration of patient follow-up after treatment ranged from 1–2 years. The results demonstrated a decrease of 10.5 PLMs/h (95% CI: −15.4 to −5.6 PLMs/h) as measured by the PLMI (see **Figure S168**). The clinical significance of this increase was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of ferrous sulfate in children with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S28**).

Benefits vs harms

The potential benefits of ferrous sulfate in children with RLS include a clinically significant reduction in disease severity. Side effects including constipation have been reported. The TF

judged that the potential benefits of ferrous sulfate in children with RLS outweigh the potential harms.

Resource use

The TF judged the costs of ferrous sulfate to be negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in disease severity, the TF judged that most children with RLS would generally be accepting of treatment with ferrous sulfate.

PICO 5: SPECIAL PEDIATRIC POPULATIONS WITH RLS

The TF did not identify any studies reporting evidence for special pediatric populations with RLS.

PICO 6: PEDIATRIC POPULATIONS WITH PLMD

The TF did not identify any studies reporting evidence for pediatric populations with PLMD.

The following interventions are those for which the TF deemed there was insufficient evidence to make a recommendation in the accompanying clinical practice guideline.[1]

PICO 1: ADULTS WITH RLS

IV iron sucrose

A total of 2 RCTs[146,147] investigated the use IV iron sucrose in adults with RLS to improve 1 or more of the following outcomes: disease severity and unwanted side effects. Participants in the RCTs received 1,000 mg of IV iron sucrose and had a mean age of 51 years (82% female). Meta-analyses were performed to assess the efficacy of IV iron sucrose as a treatment for adults with RLS. The meta-analyses are provided in **Figure S169** and **Figure S170**. A summary of findings table is provided in **Table S29**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV iron sucrose to treat adults with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of IV iron sucrose to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 RCTs[146,147] in a total of 78 participants. The duration of patient follow-up after treatment ranged from 2–11 weeks. The meta-analysis demonstrated a nonclinically significant reduction in disease severity of −1.0 points (95% CI: −5.2 to 3.3 points) as measured by the IRLS (see **Figure S169**). The certainty of evidence for disease severity was low due to imprecision.

Adverse effects: A meta-analysis of 2 RCTs[146,147] reported on the total adverse events that led to study withdrawal in a total of 78 participants. The duration of patient follow-up after treatment ranged from 2–11 weeks. The meta-analysis demonstrated a nonclinically significant risk ratio of adverse events leading to study withdrawal of 3.21 (95% CI: 0.35 to 29.11) with an absolute risk of 84 events/1,000 patients (95% CI: 9–766 events/1,000 patients) with use of IV iron sucrose (see **Figure S170**). The certainty of evidence for unwanted side effects was low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV iron sucrose in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S29**).

Benefits vs harms

The potential benefits of IV iron sucrose in adults with RLS include a nonclinically significant improvement in disease severity. The potential harms include a nonclinically significant risk of adverse events that lead to study withdrawal. No risk of augmentation was reported. The TF judged that the balance of potential benefits and harms in adults with RLS does not favor either IV iron sucrose or the comparison.

Resource use

The TF judged the costs for IV iron sucrose to be moderate.

Clonidine

One RCT[148] investigated the use of clonidine in adults with RLS to improve 1 or more of the following outcomes: PLM frequency, sleep latency, and unwanted side effects. There were no identified studies that investigated the use of clonidine to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received dosages of clonidine from 0.1–1 mg. Participants had a mean age of 45 years (73% male). Meta-analyses were performed to assess the efficacy of clonidine as a treatment for adults with RLS. The results are provided in **Figure S171** through **Figure S175**. A summary of findings table is provided in **Table S30**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of clonidine to treat adults with RLS: unwanted side effects.

Adverse effects: One RCT[148] reported on the total adverse events that led to study withdrawal in a total of 10 participants. The duration of patient follow-up after treatment was 2 weeks. The participants did not have adverse events leading to study withdrawal with use of clonidine (see **Figure S171**).

One RCT[148] reported on the incidence of sleepiness in a total of 10 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated a clinically significant risk difference of 0.50 (95% CI: 0.18–0.82) with an

absolute risk of 500 events/1,000 patients (95% CI: 180–820 events/1,000 patients) with use of clonidine (see **Figure S172**).

One RCT[148] reported on the incidence of lightheadedness in a total of 10 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated a clinically significant risk difference of 0.40 (95% CI: 0.01–0.79) with an absolute risk of 400 events/1,000 patients (95% CI: 10–790 events/1,000 patients) with use of clonidine (see **Figure S173**).

The certainty of evidence for unwanted side effects ranged from very low to low due to risk of bias associated with lack of effective blinding and imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of clonidine: PLM frequency and sleep latency.

PLM frequency: The efficacy of clonidine to decrease PLM frequency was reported in 1 RCT[148] in a total of 10 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated an increase of 12.2 PLMs/h (95% CI: −15.6 to 40.0 PLMs/h) as measured by the PLMI (see **Figure S174**). The clinical significance of this increase was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

Sleep latency: The efficacy of clonidine to decrease sleep latency was evaluated reported in 1 RCT[148] in a total of 10 participants. The duration of patient follow-up after treatment ranged was 2 weeks. Meta-analysis demonstrated a clinically significant decrease of −17.5 minutes (95% CI: −33.7 to −1.3 minutes) (see **Figure S175**). The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of clonidine in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision (see **Table S30**).

Benefits vs harms

The potential benefits of clonidine in adults with RLS include a clinically significant improvement in sleep latency. The potential harms include a clinically significant risk of sleepiness and lightheadedness that may or may not resolve over time. No risk of augmentation was reported. The TF judged that the balance of potential benefits and harms in adults with RLS does not favor either clonidine or the comparison.

Resource use

The current unit costs of clonidine is $0.07 for a 10 mg tablet.[148] The TF judged these costs to be negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with clonidine would be effective for adults with RLS.

Botulinum

A total of 2 RCTs[149,150] investigated the use of botulinum in adults with RLS to improve 1 or more of the following outcomes: disease severity and unwanted side effects. There were no identified studies that investigated the use of botulinum to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCTs had a mean age of 61 years (54% female) and were diagnosed with moderate to severe RLS. Participants received 70–320 mU botulinum toxin injection in their legs. Meta-analyses were performed to assess the efficacy of botulinum as a treatment for adults with RLS. The meta-analyses are provided in **Figure S176** and **Figure S177**. A summary of findings table is provided in **Table S31**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of botulinum to treat adults with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of botulinum to reduce disease severity as measured by the IRLS was reported in 1 RCT[150] in a total of 6 participants. The duration of patient follow-up after treatment was 12 weeks. The results demonstrated a nonclinically significant reduction in disease severity of −2.3 points (95% CI: −9.0 to 4.4 points) as measured by the IRLS (see **Figure S176**). The certainty of evidence was low due to imprecision.

Adverse effects: A meta-analysis of 2 RCTs[149,150] reported on the total adverse events that led to study withdrawal in a total of 30 participants. The duration of patient follow-up after treatment was 12 weeks. The results did not have any adverse events leading to study withdrawal (see **Figure S177**). The certainty of evidence was low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of botulinum in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with imprecision (see **Table S31**).

Benefits vs harms

The potential benefits of botulinum in adults with RLS include a nonclinically significant improvement in disease severity. The TF judged that the balance of potential benefits and harms in adults with RLS does not favor either botulinum or the comparison.

Resource use

The TF judged the costs of botulinum are moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes.

Given the limited evidence, the TF was unable to determine whether treatment with botulinum would be effective for adults with RLS.

Perampanel

One observational study[151] investigated the use of perampanel in adults with RLS to improve 1 or more of the following outcomes: disease severity and unwanted side effects. There were no identified studies that investigated the use of perampanel to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. The observational study is a prospective clinical cohort. All participants received 2–4 mg of perampanel and served as their own controls. Meta-analyses were performed to assess the efficacy of perampanel as a treatment for adults with RLS. The results are provided in **Figure S178** through **Figure S184**. A summary of findings table is provided in **Table S32**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of perampanel to treat adults with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of perampanel to reduce disease severity as measured by the IRLS reported in 1 observational study[151] in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated clinically significant reduction in disease severity of −12.2 points (95% CI: −15.1 to −9.3 points) as measured by the IRLS (see **Figure S178**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Unwanted side effects: One observational study[151] reported on the total adverse events that led to study withdrawal in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.05 (95% CI: −0.08 to 0.18) with an absolute risk of 50 events/1,000 patients (95% CI: −80 to 180 events/1,000 patients) with use of perampanel (see **Figure S179**).

One observational study[151] reported on the incidence of dizziness in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant risk difference of 0.30 (95% CI: −0.09 to 0.51) with an absolute risk of 300 events/1,000 patients (95% CI: 90–510 events/1,000 patients) with use of perampanel (see **Figure S180**).

An analysis of 1 observational study[151] reported on the incidence of somnolence in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a clinically significant risk difference of 0.10 (95% CI: −0.05 to 0.25) with an absolute risk of 100 events/1,000 patients (95% CI: −50 to 250 events/1,000) with use of perampanel (see **Figure S181**).

The certainty of evidence of disease severity was very low due to risk of bias associated with observational studies and imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of perampanel: PLM frequency, sleep latency, and WASO.

PLM frequency: The efficacy of perampanel to decrease PLM frequency was reported in 1 observational study[151] in a total of 20 participants. The duration of patient follow-up after treatment ranged was 8 weeks. The meta-analysis demonstrated a decrease of −23.4 PLMs/h (95% CI: −26.5 to −20.3 PLMs/h) as measured by the PLMI (see **Figure S182**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Sleep latency: The efficacy of perampanel to decrease sleep latency was reported in 1 observational study[151] in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant decrease of −11.9 minutes (95% CI: −18.1 to −5.7 minutes) (see **Figure S183**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

WASO: The efficacy of perampanel to decrease WASO was evaluated reported in 1 observational study[151] in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant decrease in WASO of −49.2 minutes (95% CI: −63.5 to −35.0 minutes) with perampanel (see **Figure S184**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of perampanel in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S32**).

Benefits vs harms

The potential benefits of perampanel in adults with RLS include a clinically significant improvement in disease severity, PLM frequency, sleep latency, and WASO. The potential harms include a clinically significant risk of dizziness and somnolence that may or may not resolve over time. No risk of augmentation was reported. The TF judged that the potential benefits of perampanel in adults with RLS outweigh the potential harms.

Resource use

The current unit costs of perampanel range from $17.85 for a 2 mg tablet to $35.29 for a 12 mg tablet.[34] The TF judged these costs are moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine

whether treatment with perampanel would be effective for adults with RLS.

Vitamin D

A total of 1 RCT[152] and 2 observational studies[153,154] investigated the use of vitamin D in adults with RLS to improve 1 or more of the following outcomes: disease severity. There were no identified studies that investigated the use of vitamin D to treat adults with PLMD, and children with RLS or PLMD. Participants in the RCT received dosages of 50,000 IU vitamin D and had a mean age of 43 years (69% male). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving dosages of 28,000 or 50,000 IU vitamin D. Meta-analyses were performed to assess the efficacy of vitamin D as a treatment for adults with RLS. The meta-analyses are provided in **Figure S185** and **Figure S186**. A summary of findings table is provided in **Table S33**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of vitamin D to treat adults with RLS: disease severity.

Disease severity: The efficacy of vitamin D to reduce disease severity as measured by the IRLS was reported in 1 RCT[152] in a total of 22 participants. The duration of patient follow-up after treatment was 12 weeks. The results demonstrated a clinically significant increase in disease severity of 4.2 points (95% CI: −4.1 to 12.5 points) as measured by the IRLS (see **Figure S185**). The certainty of evidence was low due to imprecision.

The efficacy of vitamin D to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 observational studies[153,154] in a total of 24 participants. The duration of patient follow-up after treatment ranged from 2–8 months. The meta-analysis demonstrated a clinically significant reduction in disease severity of −9.8 points (95% CI: −21.7 to 2.0 points) as measured by the IRLS (see **Figure S186**).

The certainty of evidence for disease severity ranged from very low to low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of vitamin D in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S33**).

Benefits vs harms

The potential benefits of vitamin D in adults with RLS include a clinically significant improvement in disease severity. The TF judged that the potential benefits of vitamin D in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs of vitamin D to be negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with vitamin D would be effective for adults with RLS.

Yoga

A total of 1 RCT[155] and 1 observational study[156] investigated the use of yoga in adults with RLS to improve 1 or more of the following outcomes: disease severity and sleep quality. There were no identified studies that investigated the use of yoga to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT completed a 12-week yoga program and had a mean age of 51 years (78% female). The observational study is a before-and-after treatment design with participants serving as their own controls and completing an 8-week yoga program. Meta-analyses were performed to assess the efficacy of yoga as a treatment for adults with RLS. The meta-analyses are provided in **Figure S187** through **Figure S189**. A summary of findings table is provided in **Table S34**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of yoga to treat adults with RLS: disease severity and sleep quality.

Disease severity: The efficacy of yoga to reduce disease severity as measured by the IRLS was reported in 1 RCT[155] in a total of 40 participants. The duration of patient follow-up after treatment was 12 weeks. The results demonstrated a clinically significant reduction in disease severity of −5.3 points (95% CI: −9.6 to −1.1 points) as measured by the IRLS (see **Figure S187**). The certainty of evidence was low due to imprecision and risk of bias associated with inadequate blinding.

Sleep quality: The efficacy of yoga to improve sleep quality was evaluated based on an analysis of 1 RCT[155] that reported on the PSQI scale in a total of 40 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a nonclinically significant improvement in sleep quality of −1.2 points (95% CI: −3.2 to 0.8 points) as measured by the PSQI scale (see **Figure S188**).

The efficacy of yoga to improve sleep quality was evaluated based on an analysis of 1 observational study[156] in a total of 10 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a clinically significant improvement in pooled sleep quality of 1.1 points (95% CI: 0.2 to 2.1 points) (see **Figure S189**).

The certainty of evidence for sleep quality ranged from very low due to risk of bias associated with observational studies and imprecision, to low due to imprecision and risk of bias associated with inadequate blinding.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of yoga in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S34**).

Benefits vs harms

The potential benefits of yoga in adults with RLS include a clinically significant improvement in disease severity and sleep quality. The TF judged that the potential benefits of yoga in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs of yoga to be moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with yoga would be effective for adults with RLS.

Acupuncture

One RCT[40] investigated the use of acupuncture in adults with RLS to improve 1 or more of the following outcomes: disease severity and sleep quality. There were no identified studies that investigated the use of acupuncture to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 10 sessions of medical acupuncture along with 300 mg of gabapentin daily. Participants in the control arm of the trial also received 300 mg of gabapentin daily. Participants had a mean age of 48 years (82% male). Meta-analyses were performed to assess the efficacy of acupuncture as a treatment for adults with RLS. The meta-analyses are provided in **Figure S190** and **Figure S191**. A summary of findings table is provided in **Table S35**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of acupuncture to treat adults with RLS: disease severity and sleep quality.

Disease severity: The efficacy of acupuncture to reduce disease severity as measured by the IRLS was reported in 1 RCT[40] in a total of 33 participants. The duration of patient follow-up after treatment was 8 weeks. The meta-analysis demonstrated a difference in disease severity of −2.5 points (95% CI: −10.0 to 5.0 points) as measured by the IRLS (see **Figure S190**). The certainty of evidence was very low due to imprecision and risk of bias associated with inadequate blinding.

Sleep quality: The efficacy of acupuncture to improve sleep quality was evaluated based on an analysis of 1 RCT[40] that reported on the PSQI scale in a total of 33 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a difference in sleep quality of 2.5 points (95% CI: −1.9 to 6.9 points) as measured by the PSQI scale (see **Figure S191**). The certainty of evidence was low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of acupuncture in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision (see **Table S35**).

Benefits vs harms

The potential benefits of acupuncture in adults with RLS include an improvement in disease severity and sleep quality, not meeting clinical significance. The TF judged that the balance of potential benefits and harms in adults with RLS does not favor either acupuncture or the comparison.

Resource use

The TF judged the costs of acupuncture to be moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with acupuncture would be effective for adults with RLS.

Cognitive behavioral therapy (CBT)

A total of 1 observational study[157] investigated the use of CBT in adults with RLS to improve 1 or more of the following outcomes: disease severity and QOL. There were no identified studies that investigated the use of CBT to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. The observational study is a prospective clinical cohort in a proof-of-concept trial. All participants received 8, 90-minute group sessions and served as their own controls. Meta-analyses were performed to assess the efficacy of CBT as a treatment for adults with RLS. The meta-analyses are provided in **Figure S192** and **Figure S193**. A summary of findings table is provided in **Table S36**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of CBT to treat adults with RLS: disease severity and QOL.

Disease severity: The efficacy of CBT to reduce disease severity as measured by the IRLS was reported in 1 observational study[157] in a total of 25 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant reduction in disease severity of −7.0 points (95% CI: −10.8 to −3.2 points) as measured by the IRLS (see **Figure S192**). The certainty of evidence for disease severity was very low to low due to risk of bias associated with observational studies and imprecision.

QOL: The efficacy of CBT to improve QOL was evaluated from an analysis of 1 observational study[157] that reported on the QOL-RLS Kohnen scale in 25 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a clinically significant improvement in QOL of −7.4 points (95% CI: −13.7 to −1.1) as measured by the QOL-RLS Kohnen scale (see **Figure S193**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of CBT in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see **Table S36**).

Benefits vs harms

The potential benefits of CBT in adults with RLS include a clinically significant improvement in disease severity and QOL. The TF judged that the potential benefits of CBT in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs of CBT to be moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with CBT would be effective for adults with RLS.

Near infrared light therapy

One RCT[158] investigated the use of near infrared light therapy in adults with RLS to improve the outcome of disease severity. There were no identified studies that investigated the use of near infrared light therapy to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 3 treatments per week for 4 weeks. Participants had a mean age of 48 years (1:1 female-to-male). Meta-analyses were performed to assess the efficacy of near infrared light therapy as a treatment for adults with RLS. The meta-analyses are provided in **Figure S194**. A summary of findings table is provided in **Table S37**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of near infrared light therapy to treat adults with RLS: disease severity.

Disease severity: The efficacy of near infrared light therapy to reduce disease severity as measured by the IRLS was reported in 1 RCT[158] in a total of 34 participants. The duration of patient follow-up after treatment was 5 weeks. The results demonstrated a clinically significant reduction in disease severity of −8.3 points (95% CI: −12.3 to −4.3 points) as measured by the IRLS (see **Figure S194**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of near infrared light therapy in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision (see **Table S37**).

Benefits vs harms

The potential benefits of near infrared light therapy in adults with RLS include a clinically significant improvement in disease severity. The TF judged the potential harms of near infrared light therapy are small. The TF judged that the potential benefits of near infrared light therapy in adults with RLS probably outweigh the potential harms.

Resource use

The unit costs of near infrared light therapy range in price between $400 and $1,200. The TF judged these costs as moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with near infrared light therapy would be effective for adults with RLS.

Tramadol

One observational study[159] investigated the use of tramadol in adults with RLS to improve 1 or more of the following outcomes: disease severity and unwanted side effects. There were no identified studies that investigated the use of tramadol to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the observational study received dosages of tramadol from 50–150 mg. Participants had a mean age of 56 years (66% female). Meta-analyses were performed to assess the efficacy of tramadol as a treatment for adults with RLS. The meta-analyses are provided in **Figure S195** through **Figure S197**. A summary of findings table is provided in **Table S38**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of tramadol to treat adults with RLS: disease severity and unwanted side effects.

Disease severity: The efficacy of tramadol to reduce disease severity as measured by the IRLS was reported in 1 observational study[159] in a total of 10 participants. The duration of patient follow-up after treatment was between 15 and 24 months. The results demonstrated a significant reduction in disease severity of −80.2 points (95% CI: −90.7 to −69.7 points) as measured by self-reported distress scale (see **Figure S195**). The certainty of

evidence was very low due to risk of bias associated with observational studies and imprecision.

Adverse effects: One observational study[159] reported on the total adverse events that led to study withdrawal in a total of 12 participants. The duration of patient follow-up after treatment was between 15 and 24 months. The results demonstrated a nonsignificant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: −0.15 to 0.15) with an absolute risk of 0 events/1,000 patients (95% CI: −150 to 150 events/1,000 patients) with use of tramadol (see **Figure S196**).

One observational study[159] reported on the incidence of dizziness in a total of 12 participants. The duration of patient follow-up after treatment was 15–24 months. The results demonstrated a nonsignificant risk difference of 0.08 (95% CI: −0.12 to 0.29) with an absolute risk of 83 events/1,000 patients (95% CI: −73 to 240 events/1,000 patients) with use of tramadol (see **Figure S197**).

The certainty of evidence for unwanted side effects was very low due to risk of bias associated with lack of effective blinding and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of tramadol in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision (see **Table S38**).

Benefits vs harms

The potential benefits of tramadol in adults with RLS include a significant improvement in disease severity. The potential harms include a risk of dizziness that may or may not resolve over time. No risk of augmentation was reported. The TF judged that the potential benefits of tramadol in adults with RLS outweigh the potential harms.

Resource use

The current unit costs of tramadol range from $0.02 for a 50 mg tablet to $2.47 for a 300 mg tablet.[27] The TF judged these costs as negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with tramadol would be effective for adults with RLS.

Transcranial magnetic stimulation

One RCT[160] investigated the use of transcranial magnetic stimulation in adults with RLS to improve disease severity. There were no identified studies that investigated the use of transcranial magnetic stimulation to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 10 treatments total, 1 every day for 3 days, across 30 days. Participants had a mean age of 56 years. Meta-analyses were performed to assess the efficacy of clonidine as a treatment for adults with RLS. The meta-analyses are provided in **Figure S198**. A summary of findings table is provided in **Table S39**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of transcranial magnetic stimulation to treat adults with RLS: disease severity.

Disease severity: The efficacy of transcranial magnetic stimulation to reduce disease severity as measured by the IRLS was reported in 1 RCT[160] in a total of 19 participants. The duration of patient follow-up after treatment was 4 weeks. The results demonstrated a clinically significant reduction in disease severity of −15.9 points (95% CI: −19.9 to −11.9 points) as measured by the IRLS (see **Figure S198**). The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of transcranial magnetic stimulation in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision (see **Table S39**).

Benefits vs harms

The potential benefits of transcranial magnetic stimulation in adults with RLS include a clinically significant improvement in disease severity. The TF judged the potential harms of transcranial magnetic stimulation are small. The TF judged that the potential benefits of transcranial magnetic stimulation in adults with RLS probably outweigh the potential harms.

Resource use

The TF judged the costs of transcranial magnetic stimulation as moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with transcranial magnetic stimulation would be effective for adults with RLS.

Transcutaneous spinal direct current stimulation

One RCT[161] investigated the use of transcutaneous spinal direct current stimulation in adults with RLS to improve 1 or more of the following outcomes: disease severity and sleep quality. There were no identified studies that investigated the use of transcutaneous spinal direct current stimulation to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 1 treatment daily, for 14 days. Participants had a mean age of 62 years (77% female). Meta-analyses were performed to assess

the efficacy of transcutaneous spinal direct current stimulation as a treatment for adults with RLS. The meta-analyses are provided in **Figure S199** and **Figure S200**. A summary of findings table is provided in **Table S40**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of transcutaneous spinal direct current stimulation to treat adults with RLS: disease severity and sleep quality.

Disease severity: The efficacy of transcutaneous spinal direct current stimulation to reduce disease severity as measured by the IRLS was reported in 1 RCT[161] in a total of 30 participants. The duration of patient follow-up after treatment was 2 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −8.4 points (95% CI: −13.6 to −3.2 points) as measured by the IRLS (see **Figure S199**). The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

Sleep quality: The efficacy of transcutaneous spinal direct current stimulation to improve sleep quality was reported in 1 RCT[161] in 30 participants that reported on the PSQI scale. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a nonclinically significant improvement in sleep quality of −1.6 points (95% CI: −4.2 to 1.0) as measured by the PSQI scale (see **Figure S200**). The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of transcutaneous spinal direct current stimulation in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision (see **Table S40**).

Benefits vs harms

The potential benefits of transcutaneous spinal direct current stimulation in adults with RLS include a clinically significant improvement in disease severity. The TF judged the potential harms of transcutaneous spinal direct current stimulation are small. The TF judged that the potential benefits of transcutaneous spinal direct current stimulation in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs of transcutaneous spinal direct current stimulation as moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with transcutaneous spinal direct current stimulation would be effective for adults with RLS.

PICO 2: ADULT POPULATIONS WITH RLS AND ESRD

IV LMW iron dextran

One RCT[162] investigated the use IV LMW iron dextran in adults with RLS and ESRD to improve 1 or more of the following outcomes: disease severity and adverse effects. Participants in the RCTs received 1,000 mg of IV iron dextran and had a mean age of 56 years (37% female). Analyses were performed to assess the efficacy of IV iron dextran as a treatment for adults with RLS and ESRD. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV LMW iron dextran to treat adults with RLS: disease severity and adverse effects.

Disease severity: The efficacy of IV iron dextran to reduce disease severity as measured by a nonvalidated disease severity score was evaluated using analysis of 1 RCT[162] in a total of 25 participants. The duration of patient follow-up after treatment was 4 weeks. The analysis demonstrated a reduction in disease severity but by 4 weeks they showed worsening in both groups. The TF was unable to determine clinician significance as the RLS scale used was not a validated tool. The certainty of evidence for disease severity was low due to imprecision.

Adverse effects: The 1 RCT[162] reported on adverse events but did not lead to study withdrawal in a total of 25 participants. The duration of patient follow-up after treatment was 4 weeks. The adverse events reported were nausea, headache, and vomiting.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV LMW iron dextran in adults with RLS and ESRD was low based on the critical outcomes and downgrading of the evidence due to imprecision.

Benefits vs harms

The potential benefits of IV LMW iron dextran in adults with RLS and ESRD include a nonclinically significant improvement in disease severity. The potential harms include a nonclinically significant risk of adverse events that lead to study withdrawal. The TF judged that the balance of potential benefits and harms in adults with RLS does not favor either IV LMW iron dextran or the comparison.

Resource use

The TF judged the costs for IV LMW iron dextran to be moderate due to costs of infusion center administration.

Patient values and preferences

The TF judged that there is probably no uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with IV LMW iron dextran would be effective for adults with RLS and ESRD.

Vitamin C + vitamin E

1 RCT[137] investigated the use of vitamin C + vitamin E in adults with RLS and ESRD to improve 1 or more of the following outcomes: disease severity. There were no identified studies that investigated the use of vitamin C + vitamin E to treat adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 200 mg vitamin C and 400 mg vitamin E. Participants had a mean age of 53 years (63% female). Meta-analyses were performed to assess the efficacy of vitamin C + vitamin E as a treatment for adults on hemodialysis with RLS. The meta-analyses are provided in **Figure S201**. A summary of findings table is provided in **Table S41**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of vitamin C + vitamin E to treat adults with RLS and ESRD: disease severity.

Disease severity: The efficacy of vitamin C + vitamin E to reduce disease severity as measured by the IRLS was reported in 1 RCT[137] in a total of 30 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant reduction in disease severity of −7.2 points (95% CI: −10.3 to −4.1 points) as measured by the IRLS (see **Figure S201**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of vitamin C + vitamin E in adults with RLS and ESRD was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S41**).

Benefits vs harms

The potential benefits of vitamin C + vitamin E in adults with RLS and ESRD include a clinically significant improvement in disease severity. The TF notes that a dose of vitamin E of 400 mg and greater may increase mortality risk in certain populations.[163,164] The TF judged that the balance of potential benefits and harms in adults with RLS and ESRD does not favor either vitamin C + vitamin E or the comparison.

Resource use

The TF judged the costs for vitamin C + vitamin E are negligible.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with vitamin C + vitamin E would be effective for adults with RLS and ESRD.

Vitamin E

One RCT[137] investigated the use of vitamin E in adults with RLS and ESRD to improve 1 or more of the following outcomes: disease severity. There were no identified studies that investigated the use of vitamin E to treat adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 400 mg vitamin E and had a mean age of 53 years (63% female). Meta-analyses were performed to assess the efficacy of vitamin E as a treatment for adults on hemodialysis with RLS. The meta-analyses are provided in **Figure S202**. A summary of findings table is provided in the **Table S42**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of vitamin E to treat adults with RLS and ESRD: disease severity.

Disease severity: The efficacy of vitamin E to reduce disease severity as measured by the IRLS was reported in 1 RCT[137] in a total of 30 participants. The duration of patient follow-up after treatment was 8 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of −7.0 points (95% CI: −10.4 to −3.6 points) as measured by the IRLS (see **Figure S202**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of vitamin E in adults with RLS and ESRD was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see **Table S42**).

Benefits vs harms

The potential benefits of vitamin E in adults with RLS and ESRD include a clinically significant improvement in disease severity. The TF notes that a dose of vitamin E of 400 mg and greater may increase mortality risk in certain populations.[163,164] The TF judged that the balance of potential benefits and harms of vitamin E in adults on hemodialysis with RLS does not favor either vitamin E or the comparison.

Resource use

The TF judged the costs for vitamin E are negligible.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF was unable to determine whether treatment with vitamin E would be effective for adults with RLS and ESRD.

OTHER INTERVENTIONS

The TF also identified studies reporting evidence for interventions in which the GRADE process was not applied, and these interventions were not considered for recommendations in the accompanying clinical practice guideline.[1] These studies had limited data on critical or important outcomes or biased study designs or methods. These interventions, in alphabetical order, are as follows: acupressure,[165] alpha-dihydroergocryptine,[166]

bromocriptine,[79,167] cannabinoids,[168] cryotherapy,[169] deep brain stimulation (in patients with Parkinson's disease),[170] exercise,[171–178] electronic stimulation,[179] foot massage,[180] heat therapy,[180] hot or cold baths,[165,181] hypericin,[182] hydrocortisone,[183] intrathecal morphine,[184] istradefylline,[185] levetiracetam (in children with attention deficit hyperactivity disorder),[186] light therapy,[187] magnesium in primary RLS,[188] magnesium (in patients with PLMD),[189,190] melatonin,[187] methadone,[191,192] olive oil massage or lavender oil massage,[193–195] pneumatic compression,[196,197] pramipexole (in patients with spinal cord injury or type II diabetes),[198,199] progressive relaxation,[200] rifaximin,[201] vibration pads,[202] vitamin B6,[190] and foot compression wrap.[196]

DISCUSSION

This systematic review delivers an updated and comprehensive assessment of published research on the treatment of RLS and PLMD in both adults and children. The use of the GRADE methodology offers a systematic approach that minimizes bias with recommendations based on the balance between the benefits and harms of each treatment intervention. Initially, the TF determined 6 PICO questions relevant to this systemic review. No studies meeting inclusion criteria were found for 2 of the 6 PICO questions (special populations of children with RLS, and children with PLMD) and 2 (children with RLS and adults with PLMD) had very few studies, leaving the majority of the analyzed studies on RLS in adults and special populations of adults with RLS.

For each PICO, the TF identified critical outcomes, and then measurement tools for each outcome. For RLS in both adults and children, disease severity was the primary focus along with sleep quality and QOL in most categories. The most heavily weighted outcome measure was the IRLS, as this tool has been used in the vast majority of clinical trials in the past 3 decades. It is a validated clinical scale, demonstrating concurrent criterion validity with the clinical global impression of severity. Further, it incorporates all 3 of these critical outcomes in 1 scale. Adverse effects were also a critical outcome shared by all 6 PICOs. Within adverse effects, the TF elected to focus on those most relevant to clinical practice, including adverse effects leading to study withdrawal to capture all major side effects. There was a focus on augmentation, drowsiness/somnolence, and dizziness, with the latter 2 being among the most common for classes of drugs with central nervous system effects. Adverse effects specific to a drug, but not shared among other drug classes, were also highlighted, such as cardiac valvulopathy in the case of cabergoline.

The development of CSTs was a challenge for this guideline as there were inadequately established relationships between treatment-related changes in scales and underlying clinical symptoms, even in the most widely employed instruments. Further, some nonvalidated measurements, including many visual analog scales, used primarily in studies predating the IRLS, could not be used at all given the lack of such validation between CST and a meaningful clinical change. Because of the wide variety of metrics available to assess aspects of RLS, some of the less utilized or clinically relevant tools were only employed when higher quality ones such as the IRLS or Epworth Sleepiness Scale were not available. As a result of these shortcomings, a small number of treatments could not be evaluated. However, the TF did not find that this affected the results of the overall recommendations.

Perhaps the biggest change from the previous systematic review in 2012[2] was the focus on augmentation as a critical adverse effect of dopaminergic medications. This assessment led to conditional recommendations against the use for all nonergotamine dopamine agonists and levodopa as initial therapy in the treatment of RLS in adults and in special populations of adults with RLS. In this systematic review, RCTs generally resulted in higher quality evidence over observational studies. However, as noted in the clinical practice guidelines,[1] augmentation is a complication that generally develops only after long-term treatment. RCT durations are generally on the order of weeks or months, rather than a year or several years that it may take for augmentation to become apparent. Thus, the vast majority of RCTs did not assess–and could not capture–augmentation. The TF analyzed augmentation incidence in the few clinical trials that did assess this outcome, but determinations were also supported by high-quality retrospective studies.

Prior to literature search, the TF sought to maintain broad inclusion criteria. Larger RCTs took precedence in the evaluation process, but observational studies with as few as 5 subjects were included. Many of the RLS treatments had very small observational or even randomized samples that met inclusion criteria but provided insufficient data for any recommendations. Other treatments had more clinical evidence, but the TF could not make any recommendation based on the available research and instead gave "no recommendation," signifying the need and encouragement for further research on these approaches. The lack of recommendation for or against these treatments should not be a barrier to use, when clinically indicated, nor should it be an obstacle to further research regarding their harms and benefits.

The systematic review includes information on PLMS, although these did not contribute to our clinical recommendations in the clinical practice guidelines.[1] Currently, the index of PLMS (PLMI) measured in polysomnography has no clear utility in the evaluation of RLS disease severity, as the 2 are poorly correlated both cross-sectionally and as changed with treatment. However, in the future, research may demonstrate that PLMI is relevant in this condition in either short- or long-term outcomes.

There were very few studies that met inclusion criteria for the treatment of PLMD in adults and none in children, and no new treatment studies were identified since the last systematic review. PLMD cannot be diagnosed unless RLS, rapid eye movement sleep behavior disorder, untreated obstructive sleep apnea, and narcolepsy are excluded in the patient. This sets a high standard for PLMD diagnosis, which makes research in this area difficult.

Within the broad category of special populations of adults with RLS, most studies meeting inclusion criteria were in adults

with RLS and comorbid chronic kidney disease/ESRD. There were no studies found for the PICO questions of special populations of children with RLS or children with PLMD. There was very little published on the treatment of RLS in children outside of oral iron supplementation, although this is an important addition to the new guidelines. Although IV iron and many of the same medications used in adults are employed clinically in children, currently there have been no published trials meeting inclusion criteria to be assessed in this systematic review.

Future directions

With widespread prescribing of dopaminergic medications over the past quarter century and a significant portion of those with RLS now having augmentation, prospective, randomized clinical trials specific to those having RLS with augmentation are needed. Studies assessing the relative efficacy and long-term safety of iron, alpha-2-delta ligands, and opioids, and their ability to allow taper and discontinuation of dopaminergic agents in such patients will be of substantial clinical value. More use of quantitative measurements of augmentation severity in such treatment trials would be particularly helpful aside from the gold-standard measurements of RLS disease severity.

Very few clinical trials were identified in this systematic review for pediatric and special populations with RLS, highlighting the need for future studies to focus on identifying the underlying causes of pediatric RLS and developing targeted treatments that address these causes. Equally, patients with RLS comorbid with other medical conditions may provide challenges for our existing clinical trial protocols and efficacy outcomes. For instance, patients with Parkinson's disease and RLS may already be taking dopaminergic agents and trials of add-on therapy may be appropriate. Further, in this population, assessment of an intervention's effect on the underlying movement disorder may be appropriate. Similarly, treatment studies with pregnant women may want to include outcomes for the pregnancy and the fetus. Beyond special populations, subtyping of RLS, for instance those with a "painful" variant of RLS, with linkage to specific genetic polymorphisms, may provide more personalized treatments.

Given the complexities in the diagnosis of PLMD, in order for high level research to be conducted on this disorder, it is critical to lay forth specific criteria for the evaluation and diagnosis of PLMD. Currently these research criteria for PLMD are being developed by a TF commissioned by the International RLS Study Group. These consensus criteria will standardize assessment for a disorder in which diagnosis has historically been challenged by numerous clinical confounders. The introduction of these criteria will allow studies to be conducted to outline prevalence of PLMD and then beyond these studies to assess efficacy of different treatments of PLMD.

RLS is a clinical diagnosis, and its severity is assessed clinically. However, objective tests would be welcome in subtyping RLS, in complementing RLS severity scales, and for assessing changes with treatment. Currently, there is ongoing research with imaging in RLS including the assessment of iron in the central nervous system, but other diagnostic techniques that may correlate with symptoms are needed as well. Further development in interpreting and employing limb movement analysis could also fill the void in objective assessment. The single night PLMI measured by polysomnography is presently lacking in utility, but devices capable of longitudinal nightly measurement of sleep-related limb movements may be coming and may provide better clinical relevance. Lastly, as RLS severity instruments are entirely obtained through self-report, it is essential that nonpharmacological treatment trials incorporate adequate masking, particularly for devices and procedures, where strong placebo effects are present.

Forty years ago, RLS was generally unknown to the medical community. The dramatic acute efficacy and associated FDA approvals of the dopaminergic agents increased awareness of RLS within both the public and medical community. Consequently, there was an initial surge of enthusiasm and satisfaction about RLS treatment. Subsequently, the discovery of clear genetic associations from large genome-wide association studies and demonstrations of brain iron deficiency (and the efficacy of iron treatments) led to optimism about progress into further translation of RLS physiology into clinical practice. However, the increasing incidence of dopaminergically-mediated iatrogenic worsening of RLS symptoms has led to a new surge of severely affected RLS patients whose treatment is now more complex and pressing. Education, such as this systematic review, about treatment options is now particularly important given that most clinicians continue to prescribe dopaminergic agents as first-line treatment for RLS. This systematic review looks back at the last 40 years with some pride at our progress, some disappointment at our naivete, but some optimism that continued research will translate into better treatments for RLS in the future.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
CBT, cognitive behavioral therapy
CGI-I, clinical global impressions-improvement scale
CGI-S, clinical global impressions-severity scale
CI, confidence interval
CST, clinical significance threshold
ER, extended-release
ESRD, end-stage renal disease
GRADE, Grading of Recommendations Assessment, Development, and Evaluation
IRLS, International RLS Study Group Severity scale
IV, intravenous
LMW, low molecular weight
MOSS, Medical Outcomes Study Sleep
PGI, patient global impression
PGI-I, patient global impression of improvement scale
PICO, patient, intervention, comparison, and outcomes
PLM, periodic limb movement
PLMD, periodic limb movement disorder
PLMI, periodic limb movement index
PLMS, periodic limb movement during sleep

PSQI, Pittsburgh Sleep Quality Index
QOL, quality of life
RCT, randomized controlled trial
RLS, restless legs syndrome
TF, task force
WASO, wake after sleep onset

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